

CATEGORIES of DISEASE

Diseases may be categorised in various ways. They may be broadly divided into mental or physical diseases, and infectious or non-infectious diseases, with sub-groups of each. Many of the categories of diseases overlap so that a single disease may appear in several categories.

Physical disease

These affect the body and its functioning in some way. They may affect one specific organ (as in coronary heart disease) or be spread throughout the whole body (as in a malaria infection). They may be temporary or permanent. As shown in the examples below, physical illnesses encompass most of the other categories, including some of the mental illnesses.

Mental disease

Now more commonly called psychiatric disorders these affect the functioning of the brain or mind. The group covers a wide spectrum of disorders including those associated with degeneration of neurones in the brains of older people leading to loss of memory and other brain faculties as in Alzheimer's disease, as well as diseases such as Schizophrenia which may lead to personality changes in younger people. Such potentially severe disorders which often prevent people from functioning in a socially acceptable manner are known as psychoses. Milder forms of mental illness where strong personality changes do not necessarily occur are termed neuroses. These include depression, and extreme anxiety (including phobias).

In the past, and indeed to some extent in the present day, mental diseases have often not received the same recognition as physical diseases in society or within the medical profession. It is, however, becoming apparent that many of these disorders are actually caused by physical changes in chemical messengers or electrical signals within the brain, which can sometimes be treated using drugs in the same way as physical diseases of the body. For example, some forms of depression caused by low levels of certain neurotransmitters in the brain can be treated using drugs which help to restore the levels of such chemicals to normal.

It is thought that some psychoses, including Schizophrenia, have a genetic component as well as a range of social, psychological and environmental components. Some also have an infectious cause: syphilis, for example, was once an important cause of severe mental illness.

Social diseases

These are a very broad category which may extend to all diseases which are influenced by people's living conditions and social interactions. In particular it includes diseases which have different distributions between different socio-economic classes. Thus it includes diseases such as TB which are made worse by poverty and overcrowding; diseases such as obesity and coronary heart disease which are most common in the lower socio-economic classes of the developed world, and diseases associated with alcohol and drug

misuse which again occur more commonly in specific sectors of society. The term ‘social disease’ could however be extended to include all diseases spread by social contact, and thus cover the sexually transmitted diseases such as gonorrhoea and a range of other infectious diseases.

Infectious diseases

These are caused by specific **pathogens** invading the body. Pathogens are organisms which cause disease and are most commonly bacteria, viruses, and fungi, although they may be single celled animals (e.g. Protocista), worms or arthropods. Some examples of infectious diseases are HIV/AIDS (caused by a virus) malaria (caused by a protocistan parasite) and TB and cholera (both caused by bacteria). All infectious diseases can be transmitted (passed on) from one person to another in some way. Infectious diseases may be transmitted via droplets of moisture in the air, through contact including sexual contact where body fluids from one partner enter the tissues of another, via vectors such as mosquitoes, and via infected food or water.

Non-infectious diseases

These are not caused by pathogens, but by other factors, such as those in the environment or in the genetic makeup of a person (inherited diseases). There are many different categories of non-infectious diseases including **deficiency diseases**, such as xerophthalmia caused by a deficiency of vitamin A, **degenerative diseases** such as coronary heart disease, **inherited diseases** such as cystic fibrosis, and **self inflicted diseases** such as lung cancer. Mental illnesses are also included in this category.

Degenerative

These appear in older people as the body begins to function less efficiently and repair mechanisms fail. They often develop over a long period of time and are often ‘multifactorial’ (have many contributing causes or factors leading to their development). They include osteoarthritis, caused by ageing of joints and bone tissue; some types of cancer; and coronary heart disease, caused by gradual narrowing of the coronary arteries as fatty deposits accumulate in them, limiting blood flow to the heart muscle. The risk of some of these degenerative diseases, especially coronary heart disease (CHD) and some cancers is increased by long term exposure to certain environmental factors. In the case of CHD these include high fat diets, smoking and lack of exercise. Genetic factors are also believed to increase the susceptibility of some individuals to CHD and some cancers.

Inherited

Alternatively known as **genetic diseases**, these are caused by mutations in the genetic material of an individual. Such diseases are passed from parent to offspring at the moment of conception having either been present in the parent or having arisen as new mutations during the production of sex cells (gametes) by the parents. Some diseases in this category arise from chromosome mutations, where individuals have too many or too few

chromosomes due to unequal meiotic divisions. An example is Down syndrome, where an extra copy of chromosome 21 affects a range of mental and physical functions in sufferers. More commonly, however, genetic diseases arise from single gene mutations, where the mutation prevents the production of a normal form of polypeptide or protein in the cells of the affected individual. This in turn can have a direct effect on the mental or physical functioning of the body. Examples are cystic fibrosis, where a gene mutation results in excess mucus production in the lungs, and haemophilia where a gene for the production of a blood clotting factor (most commonly factor VIII) is faulty.

Most inherited diseases caused by gene mutations are **recessive**, so an individual requires two identical copies of a gene before they suffer the disease. This means that healthy individuals may 'carry' genes (recessive alleles) for inherited diseases such as cystic fibrosis without showing any symptoms.

Self-inflicted

These result from behaviour known to carry a health risk. They include diseases resulting from smoking (such as lung cancer) where the health consequences are now clearly known, skin cancers resulting from sunbathing without protection when the dangers of UV light are known, and deliberate attempts to harm the body through drug overdose or physical injury.

This category is not well defined, and the inclusion of diseases here is fraught with difficulties.

Deficiency

Deficiency diseases are caused by a deficiency or lack of nutrients in the diet. This may be a lack of a major nutrient such as protein, or a lack of a specific micronutrient (vitamin or mineral). Examples of specific micronutrient deficiencies include scurvy caused by a lack of vitamin C, anaemia caused by a lack of iron, and rickets caused by a lack of vitamin D when there is insufficient exposure of the skin to sunlight.

STUDYING DISEASE: HEALTH STATISTICS

In order to put in place measures to prevent, control, treat or study disease of any kind it is vitally important to have statistical information about the disease. The collection and study of such statistics relating to patterns of disease is known as **epidemiology**.

At a basic level health statistics may give information on overall death rates in a country and allow the calculation of figures for infant mortality and life expectancy, two major indicators of the health of a population. They will generally also examine the overall number of cases of illness (**morbidity**) and death (**mortality**) from a particular disease in one year. Information from different years may be compared to show whether rates of illness or death from certain diseases are increasing, decreasing or staying at the same level over a period of time.

Usually, however, epidemiologists collect much more detailed information than simply the number of cases of a disease. This

CHECKPOINT SUMMARY

- ◆ Diseases can be categorised in different ways.
- ◆ The groupings are not mutually exclusive, so one disease may be considered in several groups.
- ◆ Broad categorisation splits diseases into physical or mental (psychiatric) diseases or infectious and non-infectious diseases.
- ◆ Narrower categories recognise social, degenerative, inherited, self inflicted and deficiency diseases.

allows them to study the disease more carefully and to set up specific disease prevention or control programmes aimed at particular target groups in the population. If a disease only occurs, for example, in older people, it is unnecessary to target the whole population. Statistical information is also essential in determining whether certain drugs, vaccinations or treatments have been effective.

Statistical studies of health data can allow **associations** between diseases and certain factors, (often known as **risk factors**) to be established. Whilst this does not actually explain the links, it can form the starting point for further research. The work of Sir Richard Doll which began in the 1950s allowed the strong statistical link between cigarette smoking and lung cancer to be established. This then led to appropriate advice being given to smokers about the risks involved, and has stimulated much research into the processes by which smoking actually causes cancers and other diseases. As with all important studies of disease this was based on the collection of very **large amounts of data** and the use of specific **statistical tests** to interpret the data.

In general the larger the data-set the the greater the validity of statistical tests as applied to epidemiological information, yet the exact nature of the data collected will vary between studies. In Doll's study a group of 40 000 men were split into groups on the basis of smoking habits. Deaths from all causes as well as from lung cancer and other respiratory diseases were recorded after 10, 20 and 40 years. This is a form of **longitudinal study** as the same individuals are studied over many years. In contrast a **cross sectional study** will collect data on a large number of individuals at one point in time.

In gathering health statistics for study, epidemiologists must structure their data collection around certain key questions. Some of these include:

- ▼ Is the disease increasing, decreasing or remaining stable over a given time period.
- ▼ What is the age distribution of the disease: is it more common in babies, children, teenagers, adults or the elderly?
- ▼ What is the sex distribution of the disease: is it more common in males or females?
- ▼ What is the geographical distribution of the disease: is it more common in towns or cities and in some regions compared to others?
- ▼ What is the distribution of the disease in relation to social class: is it more common in the richer or the poorer people?
- ▼ What is the distribution of the disease in relation to occupation: is it linked to particular types of work?

◆ CHECKPOINT SUMMARY

- ◆ The collection and study of disease/health statistics is known as epidemiology.
- ◆ Health statistics are essential to disease treatment and prevention programmes.
- ◆ Basic health statistics used to assess the overall health of a population include life expectancy and infant mortality rate.
- ◆ The number of cases of morbidity and mortality for individual diseases are also collected.
- ◆ Data can be used to establish associations between certain diseases and risk factors: e.g. between smoking and lung cancer. This may lead to research into the causes of the disease.
- ◆ Generally very large amounts of statistical data must be collected, in carefully defined studies and analysed using appropriate tests.
- ◆ Epidemiologists gathering data on a disease may consider the effects of factors such as age, sex, socio-economic group, occupation, geographical location on the disease.

HEALTH STANDARDS in the DEVELOPED and DEVELOPING WORLD

The types of diseases described above are not distributed evenly across the world. There are different patterns of disease in developing and developed countries as well as differences in the overall standards of health, which reflect biological, social and economic factors. (Enormous differences in disease experience do however exist between high and low income groups within both developed and developing countries). Broadly speaking, standards of health as measured by rates of infant mortality and life expectancy are lower in most developing countries compared to developed countries. It must, however, be borne in mind that these figures give only a crude measure of health and do not, of course, take into consideration quality of life, which is much more difficult to measure.

Developed world

If measures of infant mortality rate (number of deaths per 1000 live births amongst children aged 0-1 year) and life expectancy are used as indicators of health then most developed countries show high standards of health. In the U.K, life expectancy for women is now 80 years and for men 75 years. Infant mortality stands at under 10 deaths per 1000 births.

The main causes of illness and death in the developed world are non-infectious degenerative diseases, especially coronary heart disease, cancers, and illnesses related to smoking and alcohol. Some infectious diseases, which were the major causes of death until the mid twentieth century, still cause illness and some deaths but their importance is vastly reduced. Some infectious diseases like TB and HIV/AIDS are, however, causing increasing numbers of deaths in many developed countries. Although more difficult to measure, mental disorders, especially depression, self inflicted diseases often related to the misuse of alcohol and other drugs, and stress are all increasing. This suggests that overall health and quality of life for many people in developed countries is not as high as could be expected.

The dramatic decline in deaths from infectious disease and consequent rise in conventional standards of health in developed countries can be explained by a complex of factors experienced over the past century. These primarily include improvements in sanitation and living conditions, nutrition, education and medical care, including the availability of vaccines and antibiotics. It is worth noting that in 1910, before most of these changes were in place, life expectancy for English men was 49 years and for women 53.

Health improvements have also relied upon sustained economic growth, stability of government, reductions in birth rates (partly through availability of contraception) and the establishment, in some countries, of National Health Services offering free medical care.

Developing countries

In many developing countries there are very low standards of health. The infant mortality rate in some sub-Saharan African countries exceeds 200 deaths per 1000 births. Life expectancy of people in the same regions may be as low as 45 years. (In some southern African

◆ SPECIAL SUMMARY A

The terms developed and developing countries are frequently used to refer to high and low income regions of the world even though they are unsatisfactory terms in many respects. A developed country is generally characterised by most or all of the following features: a relatively high Gross Domestic Product (GDP), a high level of industrialisation and urbanisation, a relatively low proportion of the population engaged in agricultural work, a stable population, a high life expectancy, a low birth rate, a low infant mortality rate, relatively high standards of health and a high level of literacy. In contrast developing countries have the reverse of most of these features. It should, however, be stressed that such features will vary widely between different geographical regions of a given country and between different socio-economic groups within a country. Thus regions of some developing countries show features of developed countries and vice versa. For the purposes of this chapter developing countries will be taken to include most of Africa, Asia, South and Central America, parts of Asiatic Russia and the Pacific Islands. Developed countries primarily include Western Europe, The United States, Australia and New Zealand.

countries e.g. Zimbabwe current life expectancies of 59 years are expected to decline to 45 as HIV/AIDS kills increasing numbers of young adults). In the poorest developing countries, including most African countries, infectious diseases are the most important causes of illness and death. Respiratory infections, HIV/AIDS, diarrhoeal diseases, TB, malaria and a range of diseases associated with childbirth are the main killers. Nutritional disorders e.g. protein-energy malnutrition, anaemia and vitamin A deficiency are also common. The impact of non-infectious diseases must not, however, be overlooked. These are already the leading cause of death in many developing countries where deaths from cardiovascular disorders, smoking related illnesses and cancers are increasing rapidly. This is particularly true amongst higher income urban groups in developing countries.

The reasons why standards of health are so low in parts of the developing world are highly variable between regions, and relate mainly to social, economic and political conditions rather than geographical or biological factors. Any or all of the following factors may have a significant impact on health standards in developing countries.

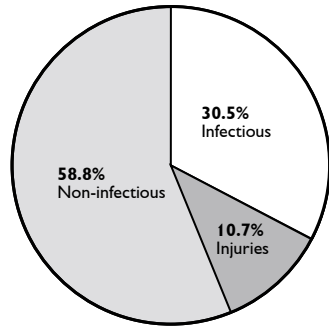
- ▼ A lack of basic sanitation (provision of clean water and toilet facilities) coupled with overcrowded conditions, particularly in large cities, encourage the spread of infectious diseases.
- ▼ Poor nutrition which may depress the immune system and increase the risk of infections.
- ▼ Insufficient medical facilities, including a lack of qualified doctors and nurses, medicines, and other essential medical equipment. These circumstances are made worse by the fact that many regions of the developing world are remote and inaccessible and transport facilities may be limited.
- ▼ A lack of basic education about hygiene and nutrition may increase the risk of some infectious and deficiency diseases
- ▼ High birth rates and inadequate maternal care lead to high rates of infant mortality.
- ▼ Civil unrest, unstable government, poor economic growth and large debts all limit spending on, and organisation of, health services.

◆ CHECKPOINT SUMMARY

- ◆ Biological, social, economic and political factors influence the pattern of diseases found across the world.
- ◆ Using life expectancy and infant mortality rate as indicators, the developed world has, on average, a better overall standard of health than the developing world. Ideally the quality of life also needs to be considered, although it is hard to measure.
- ◆ Developed countries show long life expectancy and low infant mortality. Degenerative diseases account for most deaths. Mental diseases are also a major cause of illness.
- ◆ High standards of health have been achieved in the past century due to improved nutrition, education, health services, economic prosperity and political stability.
- ◆ Developing countries have, on average, lower life expectancy and higher infant mortality. Infectious diseases remain the main cause of death in many countries but degenerative diseases are also becoming very common, especially in urban areas.
- ◆ Poor nutrition, lack of basic sanitation, low levels of education, and insufficient medical facilities, low GDP and geographical isolation are factors in low health standards.

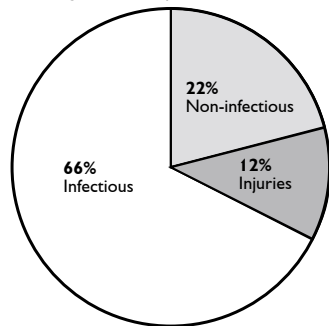
Pattern of disease distribution

Worldwide



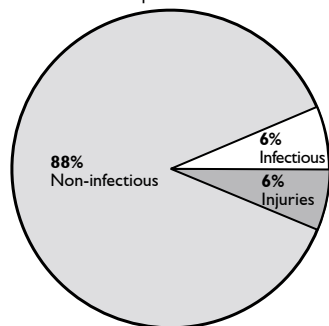
Africa

Including the world's poorest countries



Europe (West)

Including some of the richest developed countries in the world



PATTERNS of DISEASE DISTRIBUTION

The types of disease found in different countries are highly variable. Some diseases are always present and cause illness or death of large numbers of people every year. Others are always rare, and still others fluctuate wildly over time, killing many people one year and few in other years. In rare cases diseases can affect millions of people all over the world at the same time. Three broad terms are used to describe these patterns: **endemic**, **epidemic** and **pandemic**. It should be noted that the same diseases may be epidemic, endemic and pandemic at different times and in different regions, and that in epidemiology the use of these terms is usually restricted to infectious diseases.

Endemic

This is a term used to describe diseases which are common in populations all the time. An example is malaria in East Africa which kills thousands of children every year and shows relatively little variation in numbers of cases from one year to another.

Epidemics

These are defined as a short-term increase in the national incidence of a disease which is normally absent or occurs at a low level in that population. Regular influenza epidemics, such as the one in the winter of 1999, hit Britain. Cholera epidemics frequently occur during war or famine situations.

Pandemics

These are epidemics which affect most or all of the world at the same time, such as the influenza pandemic in 1918 which killed several million people worldwide and plague pandemics in the 14th century which killed up to one third of the inhabitants of Europe. There is currently an HIV/AIDS pandemic which is killing over 2.5 million people per year.

◆ CHECKPOINT SUMMARY

- ◆ An endemic disease is one which is always present in a region and causes a similar number of illnesses and deaths every year.
- ◆ Epidemics are defined as short term increases in the national incidence of a disease which normally occurs at much lower levels.
- ◆ Pandemics are epidemics which affect most or all of the world at the same time.
- ◆ The same diseases may be endemic, epidemic or pandemic depending on circumstances.

Learning Outcome (g)

The HUMAN GENOME PROJECT and its ROLE in HUMAN HEALTH and DISEASE

The Human Genome Project is a major initiative in genetics which aims to sequence the entire human genome (the entire genetic code represented by the bases A,C,T and G on all of the DNA of the 23 chromosomes of a single set). A 'rough draft' of the sequence is expected in 2000, with a final version by 2003. Automated techniques and computers have made such a vast project possible; in the past sequencing a single gene was a major undertaking.

The sequencing process will reveal the number of genes present (thought to be about 100 000, made up of 3 billion base pairs), as well as the extent of non-coding DNA that exists. Differences between individuals at the sites of genes and non-coding DNA will also be determined since the DNA of several individuals is being

sequenced for comparison. At present it seems that two given individuals taken at random from anywhere in the world share 99.9% of their DNA base sequence. Yet the 0.1% which is different still represents up to 3 million differences in the nucleotide (base) sequence both in genes and in non-coding DNA. Most of these are in the form of differences in single nucleotides (single nucleotide polymorphisms or SNPs). Some of these are important in influencing observed differences between people: not just in appearance but in their susceptibility to certain diseases. All information on the genome sequence is to be available in the public domain to allow maximum use of the information for research purposes. No gene sequences will be patented by individuals in Europe.

Impressive though the sequencing of 100 000 genes may be, this phase of the Human Genome Project should be considered as a starting point for further research on the function of the genes both in health and in illness. Progress in this field should change the way that many branches of medicine work and play a significant role in the prevention, treatment and cure of a range of diseases. Some of the ways in which such future research stemming from the human genome project may be important, are listed below.

Identification of genes associated with disease. Once the genome has been sequenced research into the relative contributions of genetic and environmental factors in disease will be possible on a larger scale than in the past. Comparisons of the DNA sequence of large groups of people with a specific disease, with controls who do not have the disease, should highlight areas of the genome where differences exist and lead researchers to genes which might be involved in the development of the disease.

In some cases a single gene may be found to cause the disease. An analysis of the pathway from faulty gene to faulty protein and disease may reveal details about the workings of cells and organs in the diseased and normal states, and so to the development of new drugs. In other cases several genes may be linked in such a way that the disease is only triggered by a particular combination of genetic and environmental factors. Genes influencing susceptibility to various types of cancer, cardiovascular disease, asthma and diabetes may be discovered, as may genes affecting the severity of certain infectious diseases like malaria, HIV and TB.

Genetic screening. If genes affecting disease susceptibility are identified then one of the applications of such research will be to improve genetic screening programmes. Whilst many people worry that the use of such screening in a non-medical setting (for example by insurance companies, or employers) might lead to discrimination against individuals on the basis of their genes there are many potential benefits which could arise from it if it is backed up by suitable genetic counselling. One such benefit is to allow the screening of babies to test for genetic diseases which may be treated or cured before harm can be caused. One current test for the genetic disease PKU detects affected individuals at birth. If these babies are fed special diets they will never suffer the severe mental and physical retardation which would otherwise affect them. Other similarly treatable conditions could be found. Screening of adults may reveal whether an individual is at risk of developing a certain disease such as diabetes or some types of cancer. In such cases doctors may be able to recommend modifications to lifestyle to reduce the risk of actually developing such a disease.

Gene therapy. Identification of gene mutations which lead to specific genetic diseases, and of mechanisms involved in switching genes on and off in cells, may stimulate further research into gene therapy. This is a branch of medicine whereby faulty genes in an individual are replaced by delivering the 'normal' form of the gene into target cells. At present such research is in its infancy and is only being trialled in adults (so called somatic gene therapy) rather than in the gametes or early stage embryo (germ line gene therapy) which would change the genes that an individual passes on. The possibility of extending such techniques to manipulate not only disease genes but genes affecting personality, intelligence, appearance and physical performance, is often raised as a negative aspect of the human genome project.

Tailor made medicines. One of the major benefits of the Human Genome Project which could be in action within the next 5-10 years is based on the concept of **pharmacogenetics**. This involves using genetic information about a patient to work out which medicines are most likely to be effective in treating their condition. It is based on the observation that there are strong genetic components both to positive drug reactions (situations where drugs work well) and negative drug reactions (side effects). For example, there are already some genes linked to hypertension (high blood pressure) and more are likely to be discovered. There are also over fifty drugs available to treat hypertension, but each patient will respond only to some of these fifty drugs owing to underlying genetic factors responsible for the condition. Using genetic information from the patient (based on variation in base sequence at SNP sites) and information from previous research, the doctor should be able to predict the best drug to use rather than using trial and error. A similar genetic test may indicate individuals at risk of serious side effects in response to vaccinations.

Genetic engineering. Human proteins like insulin and factor VIII are already produced in genetically engineered organisms for use in treating human conditions. As the human genome project identifies the location and sequence of genes coding for other essential proteins and recognises diseases resulting from faulty genes, then the use of such techniques is likely to increase. It has been suggested that genes for the production of human milk could be introduced into cows. Other future projects include the genetic manipulation of mammals to allow the production of organs for transplant into humans (xenotransplantation). Even if not identical to human organs these could be tailor-made to display particular human antigens on the surface of cells, thus preventing organ rejection.

◆ CHECKPOINT SUMMARY

- ◆ The Human Genome Project aims to have an accurate sequence of the entire human genome (genes and non-coding DNA) by the end of 2000. This is a starting point for future genetic research.
- ◆ Comparison of DNA from several individuals has so far indicated that all humans share about 99.9% of the DNA base sequence; the 0.1% difference is of great medical interest.
- ◆ The long term significance of the human genome project is enormous. It should allow for identification of disease genes, associated improvements in genetic screening, gene therapy, the rise of pharmacogenetics and advances in genetic engineering.
- ◆ Such advances should thus improve diagnosis, treatment, prevention and cure of a range of diseases with the potential to improve health standards across the world.

Diet

Content

- ▼ The concept of the balanced diet
- ▼ Energy and nutrient requirements
- ▼ Essential nutrients
- ▼ The consequences of malnutrition
- ▼ Diet and coronary heart disease

Learning Outcomes

Candidates should be able to:

- a) list the components of a balanced diet.
- b) discuss the energy and nutrient requirements of people with reference to gender, age, activity, pregnancy and lactation.
- c) explain what is meant by the term dietary reference value (DRV) and describe how these values should be used.
- d) describe the functions of essential amino acids, essential fatty acids and vitamins A and D in the body.
- e) describe the consequences of malnutrition with reference to energy and protein deficiency, anorexia nervosa, deficiencies of vitamins A and D, and obesity.
- f) discuss the possible links between diet and coronary heart disease.

Learning Outcome (a)

The BALANCED DIET

Although population groups show enormous variations in diets across the world one essential feature of human diets is the need for a relatively diverse range of foods to supply the required range of nutrients.

In order to grow and develop, maintain health, and perform various activities efficiently, the body requires the correct nutrients, in the correct amounts, on a regular basis. A diet that provides this is known as a **balanced diet** since it contains a balance of nutrients from the main food groups. The macronutrients: carbohydrates, proteins and fats, which are needed in relatively large amounts, and the micronutrients: vitamins and minerals which are needed in very small amounts. Water, is also an essential component of the diet although is not usually regarded as a nutrient. Dietary fibre (roughage or Non Starch Polysaccharides (NSP) is also an essential dietary component even though it provides no nutritional value.

Each of these nutrients, along with water and fibre has an essential role in the body, and a deficiency may result in specific disease symptoms which may be fatal. Broadly speaking the functions of these groups are as follows:

Carbohydrates and fats provide energy for the body as they are respired by cells to generate ATP for muscular contraction, cell division and growth, and to generate heat to maintain body temperature. Excess carbohydrates and fats are converted to fats in the body and used as a long-term energy store.

Proteins are required for growth and repair of cells. As discussed later, their constituent amino acids are used to produce all of the proteins required in the body, including hormones, enzymes, antibodies etc. They may also be used as an energy source in respiration but in most circumstances provide less than 20% of total energy. In starvation conditions or where a diet is high in protein but low in carbohydrates and fats, they can be a major energy source.

Vitamins are organic compounds with a wide range of functions in the body which include acting as enzyme co-factors (many of the B vitamins) and controlling many metabolic processes in cells. Some are water soluble (B vitamins, vitamin C) and cannot be stored in the body, whilst others (e.g. vitamins A and D) are fat soluble and may be stored in the liver.

Minerals are inorganic dietary components and, like vitamins, have a wide range of essential functions. Some are required for the formation of major chemicals in the body e.g. phosphorus for ATP, and iron for haemoglobin. Sodium and potassium are vital for electrical conductivity in neurones and calcium in the formation of hard bones and teeth. Calcium is also important in muscle contraction. Minerals needed in particularly small amounts are called trace elements e.g. cobalt used in vitamin B12.

Fibre is basically cellulose and related polysaccharides from plant cell walls which cannot be digested by humans. Fibre promotes the proper working of the digestive system since its bulk helps to satisfy the appetite, at the same time as aiding the movement of food through the gut by peristalsis. The transit time of food through the gut is thus reduced, which may prevent the accumulation of harmful putrefactive bacteria and consequent gut disorders including, perhaps, some cancers of the large intestine.

Water comprises 60-75% of the body weight and is essential for almost all cell functions. It forms the basis of blood and the cytoplasm of cells. An adult human cannot normally survive more than a few days without water.

The balance of the diet is important as there are many complex interactions between different foods which affect their absorption and use in the body. For example, the presence of cellulose fibres and phytic acid (found in wholemeal bread) decreases the uptake of available calcium, zinc, and iron, whereas calcium uptake is increased by vitamins D and C. A range of food types of animal and plant origin should also help to ensure that essential amino acids and fatty acids are consumed in the correct proportions. Some nutrients can be stored in the body so regular intake is less crucial whilst others cannot be stored so need to be taken more regularly to ensure optimum levels in the body.

◆ CHECKPOINT SUMMARY

- ◆ Populations show enormous variation in diets across the world, but all require the same basic nutrients.
- ◆ A balanced diet provides the correct nutrients, in the correct amounts, on a regular basis.
- ◆ Macronutrients: carbohydrates, fats, and proteins are needed in relatively large amounts.
- ◆ Micronutrients: vitamins and minerals are needed in relatively small amounts.
- ◆ Water and dietary fibre are essential components of the diet although not regarded as nutrients.
- ◆ Carbohydrates and fats supply energy.
- ◆ Proteins supply amino acids for growth and repair: Some of which are essential and must be supplied in the diet. Non-essential amino acids can be interconverted within the body from essential amino acids.
- ◆ Vitamins are essential organic compounds that must be supplied in the diet and are involved in all aspects of metabolism.
- ◆ Minerals are essential inorganic substances which have a wide range of metabolic and structural functions.
- ◆ Water is essential for all life processes.
- ◆ Fibre provides bulk to the diet for efficient movement of the food through the gut by peristalsis.
- ◆ Balance of nutrients is important due to complex interactions between their digestion and absorption in the gut.

ENERGY and NUTRIENT REQUIREMENTS

The energy and nutrient needs of an individual vary according to a number of factors. These can be considered in absolute terms (the total amount of a nutrient required by an individual) or in relative terms (the amount required per kg. of body mass). The main factors which influence requirements are: body size, gender, activity levels, age, pregnancy and lactation. These factors are discussed in more detail later.

Energy requirements

Energy intake from carbohydrates and fats is measured in Kilojoules (kJ), megajoules (MJ) or kilo calories (kcal). A kilojoule is one thousand joules, and a megajoule one million joules. A calorie is equivalent to 4.18 joules and a kilocalorie (often written Calorie with a capital C as seen on food labels) is one thousand calories.

The amount of energy required by a person per kg of body mass is dependent on two main factors: their **basal metabolic rate (BMR)** and their **activity level**.

BMR is a measure of the energy used for vital functions (neural, cardiovascular, respiratory, excretory etc) whilst the body is at complete rest in a thermoneutral environment (one in equilibrium with the body temperature). This value ranges from around 200-400 kJ/hr in adults. Variation between adults is explained by differences in body size, body composition (muscle cells have higher energy requirements than fat cells) and cellular activity associated with growth.

Activity levels may be expressed as **multiples of BMR**. A sedentary person (such as an office worker) would use only 1.4 times more energy than BMR, whilst an active one (such as an athlete) may use at least 3 times more energy than BMR.

The figures quoted below show **Estimated Average Requirements (EARS)** of energy for people of different ages and sexes. This figure is obtained by multiplying the BMR by the average physical activity level of an individual of that age. An activity level of 1.4 times BMR is used to reflect the sedentary lifestyle of most people in the UK.

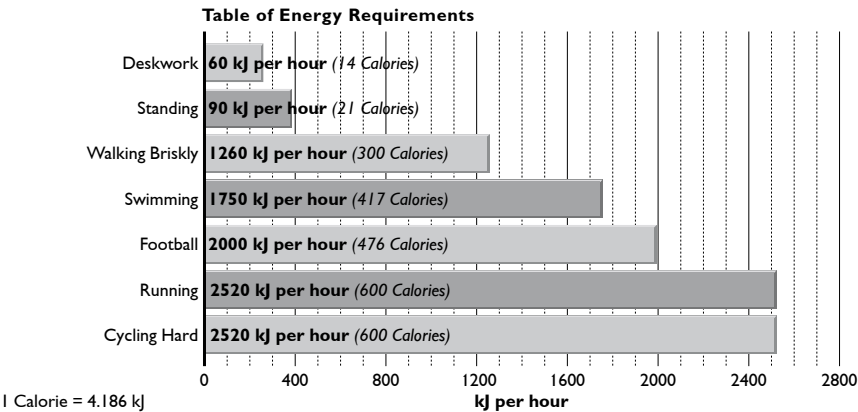


Table of energy requirements by age and sex

Estimated Average Requirements (EARs) for Energy in the UK (per day)		
Age range	EARs MJ/d (kcal/d)	
	Males	Females
0 - 3 months	2.28 (545)	2.16 (515)
4 - 6 months	2.89 (690)	2.69 (645)
7 - 9 months	3.44 (825)	3.20 (765)
10 - 12 months	3.85 (920)	3.61 (865)
1 - 3 years	5.15 (1230)	4.86 (1165)
4 - 6 years	7.16 (1715)	6.46 (1545)
7 - 10 years	8.24 (1970)	7.28 (1740)
11 - 14 years	9.27 (2220)	7.72 (1845)
15 - 18 years	11.51 (2755)	8.83 (2110)
19 - 50 years	10.60 (2550)	8.10 (1940)
51 - 59 years	10.60 (2550)	8.00 (1900)
60 - 64 years	9.93 (2380)	7.99 (1900)
65 - 74 years	9.71 (2330)	7.96 (1900)
75+ years	8.77 (2100)	7.61 (1810)
Pregnancy	+0.80* (200)	
Lactation:		
1 month	+1.90 (450)	
2 months	+2.20 (530)	
3 months	+2.40 (570)	
4—6 months	+2.20 (525)	
>6 months	+1.65 (395)	

*last trimester only. NB 1MJ = 1 megajoule. Activity based on sedentary life style (1.4 x BMR)

From Manual of Nutrition, Reference Book 342 (HMSO) 10th ed (1995)

As seen in the table, patterns of absolute energy requirement show that the larger an individual is (in terms of body mass and or height) the greater his or her energy requirement. Thus the adult man, who is on average larger than the adult woman, has a higher proportion of metabolically active cells (more muscle cells compared to fat cells), a larger heart and organs, and a higher requirement for energy. His absolute requirement will of course vary with his level of energy expenditure: the average value of 10.6 MJ or 2550 kcal for a sedentary man (1.4 x BMR) may increase to 22.7 MJ or 5464 kcal. for a highly active man (3 x BMR). A highly active woman might require 17.4 MJ compared to 8.1 MJ if sedentary. With increasing age, the daily energy requirements in both men and women decrease by up to 800kJ (200 kcals), as a result of a decrease in muscle mass, a drop in metabolic rate, and usually a decrease in activity.

If energy requirements per kg body weight are used, then young babies and children of both sexes will be seen to have the highest relative energy requirements. This reflects the fact that children are growing rapidly and growth requires energy for the synthesis of new cells and tissues creating a higher BMR. The BMR of a baby or young child may

be over twice that of an adult. A further factor is the surface area to volume ratio, which decreases with increasing size. Heat energy is lost over the surface area of the body, and the larger the surface area in relation to the volume of the body, the greater the metabolic rate required to maintain body temperature. Children over 1 year also tend to be highly active, again raising energy requirements. Adolescents, especially boys, also show high requirements due to rapid growth.

During pregnancy extra energy demands are made by the formation of the fetus and the placenta, the development of the uterus, an increase in blood volume, and an increase in storage of fat. However, a decrease in activity towards the end of the pregnancy counters this increase in BMR, so that overall there is only a slight increase in energy demand of about 0.8MJ (200 kcal) per day. The production of milk (lactation) puts a highly variable demand on the mother's food resources, but an average figure for the increased energy demands of milk production is about 2.1 MJ (500 kcal) per day.

Any individual recovering from illness or injury has a higher requirement for both protein and energy. This may allow missed growth to be 'caught up' or to allow damaged tissues (such as burns, broken bones) to be repaired. Individuals exposed to cold conditions for long periods during the day and/or night will also have a higher energy requirement than those in warmer conditions since the body uses extra energy to maintain a constant body temperature.

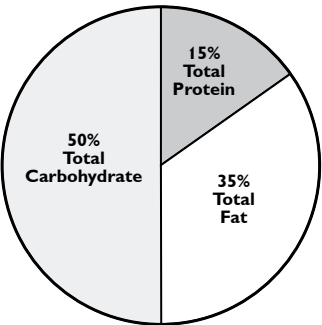
Nutrient requirements

Protein demand, relative to body mass, is highest in babies and young children with an additional peak at adolescence since protein is required for growth. In pregnant women an increase in the requirement for protein of about 6 g per day, is needed for the development of the new tissues described above. In lactating women there is also an increase in the requirement for protein of about 11 g per day, which is needed for the synthesis of milk protein. In other adults the requirement per kg body weight is slightly higher in men than women owing to greater amounts of muscle tissue. Some athletes may have an increased protein requirement but this is usually supplied along with the overall increase in energy intake. In general, individuals in developed countries eat more protein than required. It is thought that the body can adapt to low protein levels by using proteins more efficiently, which could explain why many people in the developing world exist on protein levels well below the Recommended Nutrient Intakes (RNIs) of the developed world.

Vitamin and mineral requirements are higher per kg body mass in infants and children compared to adults, as new body tissue is being synthesised. Vitamin D and calcium requirements are very closely linked to growth periods due to their roles in bone formation. The requirements for Vitamin D, Vitamin A, calcium, iron and folic acid are significantly increased during pregnancy as new fetal tissues including bones, blood and muscles are being formed. They also continue to be required at above normal levels during lactation so that milk with adequate nutrients is provided for growth of the baby.

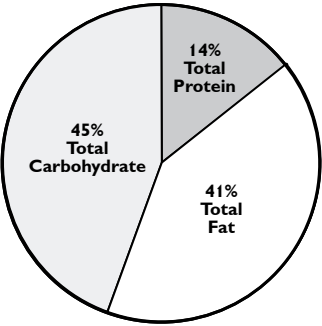
In general, women from puberty to menopause, have a higher requirement for iron to make up for the monthly losses through menstruation. Iron deficiency leading to anaemia is extremely common in women in the developing world, and is also relatively frequent in developed countries.

Suggested energy mix in UK diet 1993 (excluding alcohol)



Total Fat
saturated fatty acids 11%
monounsaturated fatty acids 13%
polyunsaturated fatty acids 6.5%

Actual energy mix in UK diet 1993 (excluding alcohol)



Total Fat
saturated fatty acids 16.1%
monounsaturated fatty acids 15.2%
polyunsaturated fatty acids 6.9%

DIETARY REFERENCE VALUES (DRVS) and their USE

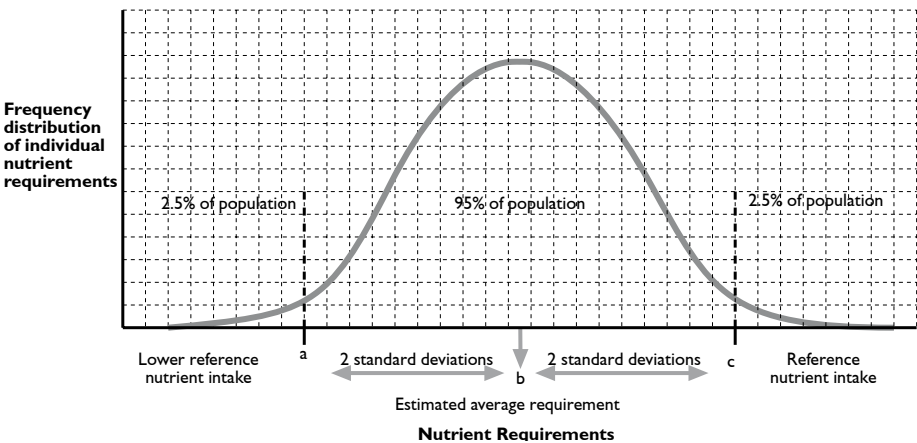
Individual variation in size, body composition and other factors means that it is impossible to give exact recommendations for the nutrient intake of a given individual. Instead population guidelines known as Dietary Reference Values (DRVs) have been established based on various measures of the range of requirements for each nutrient within a population, which are assumed to be normally distributed. Such figures, produced in 1991 by the Committee on Medical Aspects of Food Policy (COMA), are used by the government and other bodies to advise on food policy. Figures are given for each age group and both sexes within a population.

Estimated Average Requirement (EAR) of energy or protein, a vitamin or mineral. This is particularly used with reference to **energy**. 50% of the population in a given age/sex group will require more than the EAR and 50% less.

Reference Nutrient Intake (RNI). This figure for protein, minerals and vitamins represents the intake which is adequate for more than 97% of the population (2 standard deviations above the EAR). Thus if a group has an average intake at or above the RNI level it can be assumed that no-one will be deficient in that nutrient. The RNI for a group can indeed be set at the upper end of the range of requirements, as an intake moderately in excess of requirements (for protein, vitamins and minerals) has no adverse effects, but reduces the risk of deficiency. (The RNI was previously called the recommended dietary allowance (RDA).

Lower Reference Nutrient Intake (LRNI) for protein, or a vitamin or mineral is a level 2 standard deviations below the EAR. Such a level is enough for only the few people (2.5%) in a group who have naturally low needs. Intakes below this level are almost certainly inadequate for most in the population over a period of time, and an average intake in a group around the LRNI would indicate that most people would be suffering a deficiency.

Safe Intake (SI) is the range of intakes of a nutrient for which there is not enough information to estimate EAR, RNI, or LRNI. Safe intakes are given for some of the trace elements.



It should be noted that there is no RNI or LNRI for energy because excess intake leads to obesity and increases the risk of cardiovascular disease. Very low intakes can also be harmful. For this reason recommendations for energy have been set as the average of energy requirements. Further recommendations by COMA in 1991 refer to the percentage of energy intake that should come from carbohydrates and fats respectively. In 1990 40% of the daily energy intake of a British adult came from fat and 40% from carbohydrate. Recommended levels are 33% from fat and 47% from carbohydrates. Within this there are recommendations for low levels of saturated fats and refined sugars compared to unsaturated fats and starches. Most of the remainder will come from proteins (up to 20 per cent of the daily energy requirements).

Uses of Dietary Reference Values

There are several uses of Dietary Reference Values.

Dietary planning. Although DRVs are not suitable for judging whether an existing diet is suitable for an individual they can be used to plan a diet for a person or group of people in an institution (such as a boarding school or hospital). If RNIs are followed for protein, minerals and vitamins, very few deficiencies should occur. Pregnant women are examples of individuals who might be advised to ensure that they meet the RNI for folic acid, calcium and other nutrients. Patients with mild anaemia would be encouraged to meet the RNI for iron. Planning energy intake is much more difficult.

Assessing diets (of groups). Assessing the levels of nutrient intake in a population and comparing them to DRVs can give information about possible nutrient deficiencies in that population. This may lead to specific interventions. A large number of studies in developing countries have indicated low intakes of protein and energy in groups of children and pregnant women, leading to supplementation programmes.

Labelling of food products. Many processed foods carry nutritional information on the packets to allow individuals to gauge their nutritional value. Most breakfast cereals will quote the percentage of **recommended daily intake (RDI)** of a range of minerals and vitamins which would be provided by a standard serving. Most still use the term RDA although COMA suggests that they use figures based on Estimated Average Requirement. Energy requirements are not quoted although levels of energy per 100g are often given as a percentage of energy from fat (saturated and unsaturated) and carbohydrate. Knowledge of RNIs may also allow the manufacturers to add appropriate levels of vitamins and minerals to their products.

Agriculture and economics. On a larger scale, DRVs can be used to make predictions about food requirements for whole countries or regions and so influence agricultural and economic policies. Previous versions of nutrient requirements were used by the British Government to plan food policy (including rationing) during the Second World War.

◆ CHECKPOINT SUMMARY

- ◆ Energy and nutrient requirements vary with gender, age, activity, pregnancy and lactation.
- ◆ Males are generally larger than females and have a greater proportion of muscle, and thus a greater metabolic rate.
- ◆ Metabolic rate and activity fall with age, often resulting in gain in body mass.
- ◆ Activity levels may be expressed as multiples of the Basal Metabolic Rate (the BMR at rest).
- ◆ Energy requirements are expressed as Estimated Average Requirements (EARs) obtained by multiplying the BMR by the average physical activity level of an individual of a particular age group.
- ◆ Dietary Reference Values (DRVs) are based on the range of requirements for each nutrient within a population, which is assumed to be normally distributed.
- ◆ Estimated Average Requirements (EAR) will satisfy the requirements for half the population in a given group.
- ◆ Reference Nutrient Intake (RNI) will satisfy the requirement for protein, minerals, and vitamins for more than 97% of a given population.
- ◆ Lower Reference Nutrient Intake (LRNI) for protein, minerals, and vitamins are sufficient for only 2.5% of a given population.
- ◆ Safe Intakes are estimated where there is not enough information to derive EARs, RNIs, or LNRI.
- ◆ RNIs and LNRI are not given for energy requirements.

FUNCTIONS of ESSENTIAL NUTRIENTS

In a literal sense all nutrients are essential, but nutritionists use the term ‘essential nutrient’ to refer to those which must be present in the diet for the maintenance of health. ‘Non-essential nutrients’, need not be present in the diet because their lack can be compensated for by the metabolism of the body. For example the lack of sugars in the diet is compensated for by sugars provided by the digestion of starch.

Essential amino acids

Whilst each of the twenty amino acids has its own specific function, only 8 of these are required in the diet of an adult (10 in a child) as they cannot be made in the body, or made in sufficient quantities to meet requirements. These are the **essential amino acids** and include phenylalanine, valine, tryptophan, threonine, lysine, leucine, isoleucine, and methionine. The other 12 (**non-essential amino acids**) can be synthesised in the liver by the process of transamination (transferring amino groups between molecules).

Proteins which contain all of the essential amino acids are known as **proteins of high biological value** (previously first class proteins). These include many animal proteins including meats and dairy products as well as some plant proteins such as soya. Proteins from most plant sources do not, however, yield the full range of essential amino acids in sufficient amounts. Therefore they are known as second class proteins or **proteins of low biological value**. A balanced mixture of plant proteins can, however, yield a full range of essential amino acids in sufficient quantities.

Essential fatty acids

Fatty acids are derived from polyunsaturated fats in the diet. Whilst fats are primarily associated with energy supply, the fatty acid components have numerous other roles within the body. Of the many types of fatty acids, two are known as **essential fatty acids**. These can be found in most plant-derived oils and are capable of being stored in the body, therefore deficiencies are rare.

Many functions are associated with these two essential fatty acids. As well as being involved in the formation of phospholipids, the main component of the cell membrane, they are also thought to play a regulatory role in the transport and processing of cholesterol in the body. This is very important as cholesterol is required for the production of vitamin D and some hormones. Linolenic acid is required for development of the brain and retina and may also play a role in reducing the risk of blood clotting within arteries.

Vitamins

These are a group of unrelated organic chemicals which are extremely important in promoting and maintaining normal growth, development, reproduction and general health. Without them specific deficiency symptoms occur which may seriously threaten health. It is, however, difficult to assess the exact amount of vitamins required in a diet. Two examples of vitamins whose roles are relatively well understood are vitamins A and D.

Vitamin A or retinol is a fat soluble vitamin which is found in animal products (particularly liver, fish liver oils, and milk) and as a **precursor** (a substance which is converted into the required product, in this case beta-carotene) in some vegetables, including carrots, spinach and watercress. Daily recommended intakes stand at around 700 µg, although considerable amounts of the vitamin can be stored in the liver. Vitamin A has three main functions in the body: to form the light absorbing pigment retinol, a component of rhodopsin found in the rod cells of the eye; to aid the development and maintenance of healthy skin and epithelial (surface) tissue, including that of the mucous membranes of the lungs and gut; and to promote healthy growth and bone formation in children.

During pregnancy, vitamin A is required for the growth and maintenance of new maternal tissue and of the fetus although excess vitamin A can be toxic to the developing fetus, so extra supplements are not recommended. During lactation the diet should be supplemented by 350 µg per day (58% increase of normal intake) to ensure an adequate supply in breast milk.

As discussed later, the most serious consequences of a deficiency of vitamin A are night blindness, drying of the conjunctiva and permanent damage of the cornea of the eye.

Vitamin D or calciferol is a fat soluble vitamin which can be obtained in two ways. It is found in some foods, particularly eggs, dairy products and some oily fish, but it is mainly obtained through the action of UV light (sunlight) on the skin which converts a cholesterol-based precursor molecule into vitamin D. The vitamin can also be stored in the liver which is important since in Britain and other low latitudes there is little sunlight of suitable wavelength to stimulate its production in winter months.

Vitamin D controls calcium metabolism in the body, balancing calcium gain (via absorption of dietary calcium) with calcium loss (by excretion from the kidneys) and allowing an exchange of calcium between the blood and the bones. Its two main functions are to increase the absorption of calcium from the gut; and to increase calcification of bones and promote efficient use of calcium (as calcium phosphate) in bone deposition and reabsorption. This allows bones to be constantly remodelled to remain strong and to adapt to changes in body mass and other stresses. During pregnancy increased levels of Vitamin D are required to allow formation of bones and teeth in the fetus. A lactating woman also has an increased requirement as vitamin D is supplied to the baby via breast milk. Prolonged deficiencies will lead to bone deformities including **rickets** and **osteomalacia** as discussed below. Excess vitamin D is poisonous and can cause kidney failure.

◆ CHECKPOINT SUMMARY

- ◆ Essential nutrients are those which must be present in the diet for the maintenance of health.
- ◆ 8 amino acids are essential in adults (10 in children), the other 12 (10 in children) amino acids can be synthesised in the liver from the essential amino acids.
- ◆ Proteins containing all the essential amino acids are known as 'proteins of high biological value'.
- ◆ There are two essential fatty acids, both of which are polyunsaturated.
- ◆ Vitamin A (retinol) is essential for the visual pigment rhodopsin in the retina, for healthy skin and epithelia, and growth and bone formation in children. Excess can be toxic.
- ◆ Vitamin D or calciferol is found especially in eggs, dairy products, and some oily fish; but is also formed by the action of UV light on the skin. It is essential for strong bones and teeth. Excess can be toxic.

Reference Nutrient Intakes for Vitamins			
Age	Vitamin C	Vitamin A	Vitamin D
	mg/day	mg/day	mg/day
0-3 months	25	350	8.5
4-6 months	25	350	8.5
7-9 months	25	350	7.0
10-12 months	25	350	7.0
1-3 years	30	400	7.0
4-6 years	30	400	-
7-10 years	30	500	-
Males			
11-14 years	35	600	-
15-18 years	40	700	-
19-65 years	40	700	-
65+ years	40	700	10.0
Females			
11-14 years	35	600	-
15-18 years	4	600	-
19-65 years	40	600	-
65+ years	40	700	10.0
Pregnancy	+10	+100	10
Lactation:			
0-4 months	+30	+350	10
4+ months	+30	+350	10

MALNUTRITION

Strictly speaking malnutrition means ‘poor nutrition’. It may include diets where nutrients are deficient (under nutrition) as well as those where nutrients are taken in excess (over nutrition). Both macro and micronutrients can be deficient or present in excess in a diet, and in all cases specific types of malnutrition are characterised by specific symptoms.

Protein energy malnutrition (PEM)

PEM is a term used to describe cases where the diet is severely deficient in both energy sources (fats and carbohydrates) and proteins, leading to specific deficiency symptoms. It is a common disease in many developing countries, particularly those where famines or civil wars have disrupted food production and distribution. In 1999 over a quarter of a million people, mainly children, died of PEM worldwide. PEM is much more common amongst children than adults, since children have smaller reserves in terms of fat stores, as well as higher energy and protein

requirements per kg body weight. PEM is rare in the developed world although may be seen in some groups including the homeless, drug addicts and some elderly people. If PEM persists for long periods of time, particularly in children, some or all of the following may result.

- ▼ Shorter stature (low weight for age)
- ▼ A wasted or emaciated body (low weight for height).
- ▼ The immune system may cease to function efficiently, making individuals more susceptible to infections.
- ▼ Tiredness and lethargy, brain growth and development may be retarded or permanently affected by severe PEM. Learning may be affected.
- ▼ Deficiencies of specific vitamins and minerals owing to low overall food intake, often with greatly reduced variety of foods.
- ▼ Severe and prolonged PEM can lead to organ failure and death.

Whilst some of the symptoms of PEM can be easily reversed once an adequate diet is available, PEM in childhood can have long term consequences. In many cases children who have been malnourished do not 'catch up' in growth terms and end up as smaller adults. This can affect their ability to perform hard manual tasks.

Whilst protein and energy deficiency have been discussed together here, previous classifications of malnutrition have recognised two distinct forms: **kwashiorkor** where protein deficiency occurred but energy was adequate, and **marasmus** where both were severely lacking. Kwashiorkor, was characterised by stunted growth (low height for age) and the presence of **oedema** (tissue fluid accumulating beneath the skin). This is thought to relate to the lack of proteins in the blood and leads to swollen cheeks, abdomen, feet, lower legs and hands. In contrast, marasmus, resembles an extreme form of PEM as described above where weight for age is only 60% of the expected value. It is now recognised that these two conditions are not clear cut and the term PEM is now used to cover both forms.

Anorexia nervosa

Anorexia nervosa literally means 'loss of appetite through nervous causes', although this description is not strictly accurate as the disease does not necessarily involve a loss of appetite. The disease is characterised by an obsessive desire to lose weight and become thinner. This is achieved through a combination of reduced food intake, and increased exercise. Sometimes vomiting and laxatives are used to rid the body of excess food which has been eaten. During this process the body image of the sufferer becomes distorted and they may perceive themselves to be fat even though their body weight is very low. At the same time, sufferers are often obsessed by food. Anorexia is thus a serious and specific disease with a psychological component, and not simply an extreme example of slimming for health or other reasons.

Anorexia nervosa primarily affects teenage girls from upper and middle class backgrounds in developed countries, although it does occur in boys, and has been noted in children as young as 6 years as well as in some adults. Some current estimates suggest that 1 in 100 adolescent girls will be affected by the disease. Whilst it is not a new disease, its frequency has increased dramatically in recent years. Anorexia may also co-exist with bulimia, another eating disorder.

The causes of anorexia are poorly understood, but it is regarded as a mental or psychological disorder, with a suggestion of some predisposing biological (genetic, hormonal) factors and social factors. Psychologists believe that the onset of the disease in adolescence may be linked to a subconscious desire to escape from the mental and physical changes to the body that occur at this time. Another theory is that it is linked to a conscious desire by individuals to take control of one aspect of their lives. Suggested triggers are stresses of relationships, low self esteem and failure in some areas of life. Once a teenager starts to become anorexic, hormone levels in the body fall and physical and mental growth and development may be halted. Initial success in achieving weight loss may reinforce attempts to continue.

Diagnostic criteria for anorexia nervosa include the following features:

- ▼ Body weight at least 15% lower than expected weight for age and height. This may be through weight loss or through failure to gain weight during growth periods
- ▼ An intense fear of gaining weight and a overwhelming desire to be thin
- ▼ Distorted perception of the body, and of the potential seriousness of the illness
- ▼ In girls, absence of at least three consecutive menstrual cycles (amenorrhoea.)

Consequences of anorexia nervosa

Common features of anorexia which have a detrimental effect on the body in both the short and long term are listed below.

- ▼ Reduced fertility in women. The low body weight of anorexia causes amenorrhoea and the menstrual cycle may continue to be affected even if weight is gained.
- ▼ Social isolation. This often occurs during the disease as sufferers shun social occasions where eating and drinking are involved.
- ▼ Organ damage. If anorexia continues for long periods then the kidneys, heart and other organs may fail through the stress placed on the body by low food intake, and may lead to death in about 3% of patients.
- ▼ Poor thermoregulation leading to low body temperature as subcutaneous fat is lost.

If vomiting and laxative use have been common features then the following may also occur:

- ▼ Dental problems caused by excessive vomiting and hence acid damage to tooth enamel.
- ▼ Bowel problems through the excessive use of laxatives.
- ▼ Mineral deficiencies through low intake and loss via vomiting and laxative abuse.

Anorexia nervosa is difficult to treat as its causes are not well understood and it is estimated that 60% of anorexia patients are left with long term consequences, both biological and psychological.

Vitamin A deficiency

As discussed previously the main functions of vitamin A relate to its roles in the formation of rhodopsin, in the maintenance of healthy skin and epithelial tissue, and in promoting growth. A prolonged deficiency of vitamin A will thus affect all three of these essential functions.

The three most common manifestations of vitamin A deficiency are set out below.

Nightblindness. Since Vitamin A is an essential to the functioning of rod cells in the retina, a deficiency will lead to poor adaptation to dim light where rod cells are most important.

Xerophthalmia or drying of the conjunctiva and cornea. Spots of keratinised epithelial cells (cells impregnated with keratin, the protein which makes dead skin hard) accumulate on the surface of the conjunctiva, and ulcers may occur on the cornea which are susceptible to infection by micro-organisms. Eventually these changes can cause blindness. It is estimated that 250 000 children per year become blind through vitamin A deficiency in developing countries.

Thickening and drying of the skin

Vitamin D deficiency

Since the main function of vitamin D is to control calcium metabolism in the body, deficiencies of the vitamin can have serious effects on bone growth and development. A lack of vitamin D in childhood (and indeed before birth when the vitamin is essential) can lead to the disease **rickets**. Rickets is a disease where low vitamin D levels mean that too little calcium and phosphate is added to growing bones. Bones may grow slowly and will also lack strength, and may be unable to support the body weight of the child. The legs bow under the strain and the spine and pelvis may also become bent and deformed. In severe cases this can make walking very difficult or impossible.

This condition is now relatively rare in the developed world, (partly due to the addition of vitamin D to many foods, including some dairy products and bread), although it was once common. As recently as the 1960s one study showed that 9% of children in Glasgow in Scotland showed symptoms. It is still relatively common across the developing world, even in regions where there are high levels of sunlight. There are thought to be two main reasons for this: firstly in some societies babies and children (especially girls in Muslim societies) may be tightly swaddled in clothes to shield them from the sun or kept indoors. Secondly, some staple foods, including Chapatti flour, contain substances which prevent the absorption of both calcium and dietary vitamin D. Asian children in the UK are at a higher risk of rickets than white children owing to lower levels of UV light absorption by darker skin, as well as dietary and socio-cultural factors.

In adults a deficiency of vitamin D leads to **osteomalacia**, a condition in which bones become weak and soft as they lose calcium. This can lead to bone and muscle pain and to fractures of bones, particularly the hip.

Obesity

In medical terms a person is said to be overweight if their weight is more than 10% higher than the average for their height, and obese if their weight is over 20% higher than the average. Alternatively **body mass index (BMI)** which is: $\text{weight in kg}/(\text{height in m}^2)$ can be used, with a BMI of 20-25 considered ideal. An obese man would have a BMI of 30 or more, a woman 28 or more.

Obesity is very common in Britain and other developed countries, far overshadowing the importance of any other nutritional disorders. Currently up to 30% of adults in England are defined as obese using these criteria, with an additional 40% of men and 26% of women being overweight. Perhaps surprisingly obesity is more common in the lower social classes in Britain. A growing proportion of children are also affected.

Causes of obesity may include physiological causes (such as an underactive thyroid gland) or be governed by a rare hereditary defect (e.g. Prader-Willi syndrome). Generally, however, it is the result of too much food and too little exercise. The foods taken in can be of any type: protein, fats, or carbohydrates as all can be converted to body fat. Many drinks, including soft drinks, beer and wine are also high in energy. Thus, in simple terms obesity arises when energy intake exceeds energy expenditure over an extended period. In fact, the latter factor (energy expenditure) is becoming increasingly significant: whilst the average calorie intake per person in the UK declined through the 1990s, the number of obese people increased.

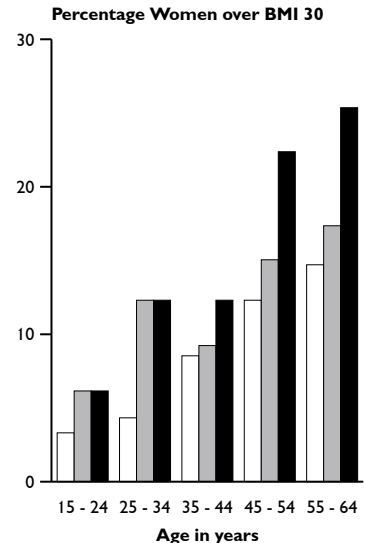
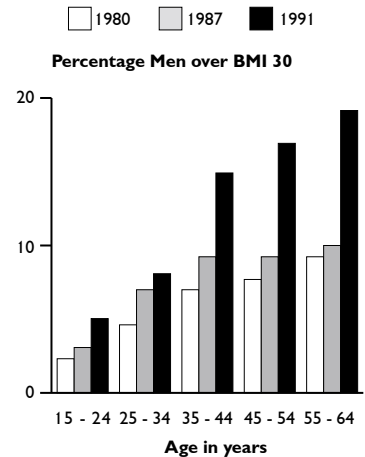
Environmental factors such as home environment are very significant in determining the likelihood of obesity. Children growing up with parents who are overweight are much more likely to become overweight themselves, even if they are adopted children who share no genetic similarities. Stress and depression may also lead to obesity in some people.

Consequences of obesity include:

- ▼ Damage to bones and joints. Excess body weight can put strain on the skeleton, leading to osteoarthritis, slipped discs and back problems. In general movement becomes more restricted and accidents may happen.
- ▼ Increased frequency of some cancers, including cancer of the gall bladder and intestine in men, and cancer of the ovaries and breast in women.
- ▼ Increased risk of cardiovascular disease, including high blood pressure (hypertension), atherosclerosis, thrombosis and myocardial infarction.
- ▼ Increased risk of type II diabetes, which seems to occur because obesity decreases sensitivity to the hormone insulin. This is itself linked to increased risk of cardiovascular disease.
- ▼ Psychological effects through loss of self esteem, teasing or bullying. May lead to depression and even suicide.

Most of the risk factors associated with obesity contribute to a shorter life expectancy in obese people compared to people of normal weight. For example a middle aged person who weighs 20% more than average has a 25% greater risk of death. Whilst this risk will be reduced again if weight is lost, the process of losing weight is lengthy and often proves very difficult.

Increasing levels of obesity



DIET and CORONARY HEART DISEASE

The cardiovascular system includes the heart and the blood vessels through which blood is pumped around the body. Cardiovascular disease is a term which covers several different diseases within this system, including **hypertension** (high blood pressure) **atherosclerosis** (narrowing of arteries with fatty deposits) and **coronary heart disease (CHD)**, a condition where fatty deposits (**atheroma**) that build up in coronary arteries can deprive the heart muscle of oxygen, leading to a heart attack. These three conditions are closely linked to each other and are all very common amongst adults in the developed world. Together they represent the main cause of death in British adults with around 110 000 people dying of CHD each year, and an additional 260 000 from strokes resulting from atherosclerosis.

Atherosclerosis is a condition in which the large arteries of the body become hardened and narrowed by the build up of deposits inside the artery wall. These deposits, which are known as atheroma (plural: atheromata) or **plaques** are composed primarily of cholesterol and other fatty materials, which are derived from the blood plasma. When atheroma builds up in the coronary arteries which supply the heart muscle, this condition and its associated effects, is known as CHD. Whilst atherosclerosis is usually only found in adults, atheroma deposits may start to build up from childhood.

Although the underlying mechanisms are not fully understood, atheroma build up is thought to begin in areas of the arteries which have been damaged in some way. Damage to the inner lining or **endothelium** may be caused by high blood pressure and overstretching of the artery walls or through chemicals derived from cigarette smoking, allowing lipids (especially cholesterol) in the plasma to enter the artery wall. The lipids accumulate beneath the smooth muscle layer, appearing initially as small fatty streaks which later become fibrous and hardened as connective tissue grows around the site. The artery wall will thus start to bulge into the cavity (lumen) of the vessel.

The effects of atherosclerosis include hypertension and thrombosis. **Hypertension or high blood pressure** may be both a cause and a consequence of atherosclerosis. While the links between the two are not well understood atherosclerosis is thought to increase the risk of hypertension by increasing resistance to blood flow in two main ways. Firstly, atheromata increase friction between the blood and the lining (endothelium) of the artery, and secondly atheromata may reduce the elasticity of arteries (see section 5.2.3).

Thromboses (singular thrombus) are internal blood clots and are another major complication of atherosclerosis. Formation of a thrombus may be started if atheroma deposits in an artery wall rupture, exposing underlying connective tissue, to which blood platelets are attracted and stick. These platelets may then change their shape and nature, and secrete chemicals causing further platelets to stick to them, gradually forming a thrombus by means of mechanisms similar to that of blood clotting at a wound site.

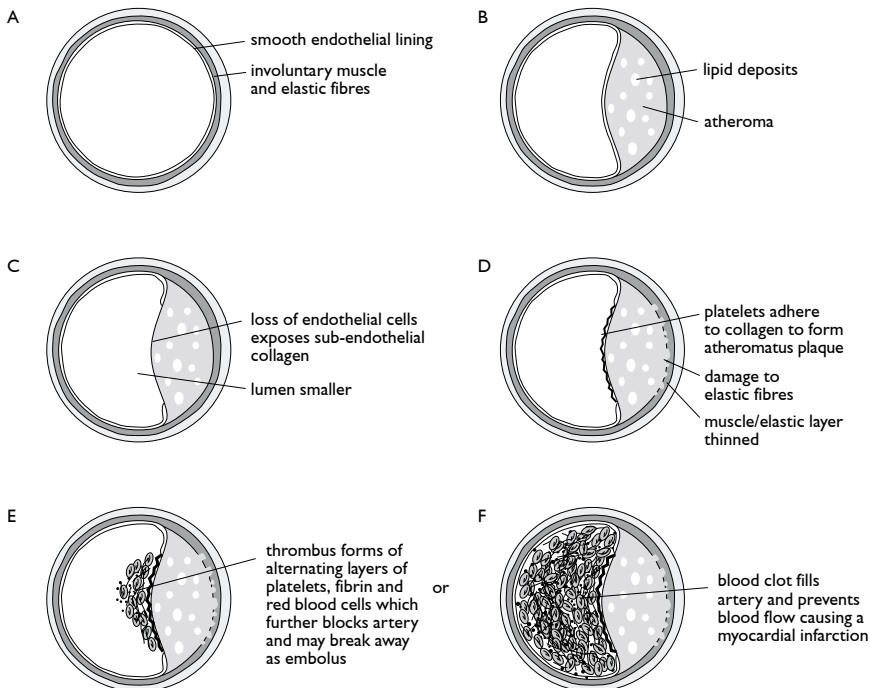
Once formed, the thrombus may cause damage in one of two ways. Firstly it may completely obstruct (block) the artery, preventing blood flow to areas of tissue. If the blockage occurs in a coronary artery

then this can lead to a heart attack or **myocardial infarction**, which occurs when parts of the heart muscle are starved of oxygen and glucose. Without oxygen and glucose the muscle tissue cannot respire and thus has no ATP for contraction of the muscle fibres. The heart then fails to contract properly which may be fatal.

Death of cardiac muscle in the heart wall (myocardial infarction), typically in the left ventricle, may occur suddenly without prior warning or may be preceded by pain in the chest region (**angina**). This pain is caused by narrowing of the coronary arteries and their inability to supply adequate oxygen to heart muscle and may be noted during exercise. Individuals suffering from angina will be carefully monitored and treated, to reduce the risk of myocardial infarction, through changes in diet and exercise and/or by drug treatment and occasionally by surgery (see section 5.2.4)

In other cases the thrombus may detach itself from the artery wall and enter the circulation. Known as an **embolus** this clot may then block a vessel in another part of the body. Clots may lodge in the pulmonary artery forming a pulmonary embolus, or in vessels of the brain leading to a stroke. Such blockages of vessels can lead to death, but if detected can be treated by giving drugs to break down the clot. People at risk of thrombosis may be given drugs such as warfarin (also used as a rat poison) or heparin which reduce blood clotting.

Thrombosis Development in Coronary Artery



Risk factors in coronary heart disease. There are a number of risk factors associated with CHD (it is said to be a multi-factorial disease). None of them are sufficient to bring about the disease on their own. Most act over a long period of time, and whilst some are avoidable, others, such as old age, are, of course, unavoidable. Some of the major factors are set out below:

- ▼ Genetic predisposition. One such example results in high cholesterol levels even when fat intake is low.
- ▼ Cigarette smoking. Chemicals in cigarette smoke are linked to artery damage and formation of atheroma.
- ▼ Hypertension or high blood pressure. Can damage walls of arteries and may play a role in initiating atheroma formation.
- ▼ Lack of exercise. Exercise helps to prevent obesity, and may reduce levels of LDLs in the blood (see section 5.2.3).
- ▼ Age. CHD is much more common in people over 40, although the accumulation of atheroma may begin in childhood.
- ▼ Gender. CHD is much more common in men than women in middle age.
- ▼ Obesity. Obese people are at higher risk due to increased blood pressure, increased strain on the heart.
- ▼ Dietary factors include high fat leading to high levels of cholesterol in blood plasma, also low fibre, high sugar, and high salt intake which is linked with raised blood pressure.

Whilst diet is only one of many risk factors in CHD, it is clearly a very important one and one which can be modified relatively easily to reduce risk.

A diet high in saturated fats (which are found mainly in foods of animal origin including dairy products and meat) can increase the risk of atheroma build up in arteries including coronary arteries by raising the level of blood cholesterol. There is a strong positive association between high levels of cholesterol and other saturated fats in the blood, and risk of CHD. Such lipids do not exist free in the blood but in compounds of lipid and protein known as Low Density Lipoproteins (LDL). LDLs are harmful as they are attracted to areas of vessel damage and can initiate the formation of atheroma.

In contrast, molecules known as HDLs-High Density Lipoproteins are formed when unsaturated fats combine with carrier proteins in the blood. High levels of HDLs seem to have a protective effect in CHD.

It should be noted that genetic factors as well as dietary factors play a role in determining the proportion of LDLs and HDLs in the blood. Some individuals eat a low cholesterol diet yet have unexpectedly high levels of LDLs in their blood, and need to monitor their diet with extra care.

Traditional Mediterranean diets are low in saturated fats, high in unsaturated fats (especially olive oil), high in fibre (from fresh fruits and vegetables), low in refined sugar and salt (due to a low intake of processed foods), with a moderate intake of red wine. In recent years it has been noted that people in Mediterranean regions (e.g. Greece and Italy) eating a traditional diet suffer much less from CHD than do people in Britain even though they have similar risk factors in terms of total food intake, smoking, and exercise levels. Such diets, or components of them, including 5 portions of fresh fruit and vegetables per day, are now recommended as one way of reducing the risk of CHD.

High fibre intake (from fruits, vegetables and whole grains) is thought to be beneficial in that it lowers levels of LDLs in the blood, perhaps through reducing absorption of lipids in the gut. Low sugar seems to be important in reducing the risk of diabetes which is itself a risk factor in hypertension and CHD, whilst high salt levels are thought to be important risk factors in hypertension. Red wine contains compounds known as 'antioxidants' which are thought to reduce the harmful effects of LDLs in the blood.

◆ CHECKPOINT SUMMARY

- ◆ Protein and energy deficiencies frequently occur together as Protein Energy Malnutrition (PEM).
- ◆ PEM more common in children due to their smaller reserves and higher requirements. PEM in children has consequences for the rest of their lives.
- ◆ Anorexia nervosa is characterised by an obsessive desire to lose weight, and a distorted self-image, and is more common in adolescent girls in developed countries.
- ◆ Anorexia nervosa is a mental (psychological) disorder, involving predisposing biological and social factors.
- ◆ Vitamin A deficiency results in nightblindness, drying of the surface tissues of the eye (xerophthalmia) leading to blindness, and thickening and drying of the skin.
- ◆ Vitamin D deficiency results in poor bone growth and development in the young (rickets). In adults deficiency results in softening of the bones as they lose calcium (osteomalacia).
- ◆ Obesity is defined as being 20% heavier than the average for the particular group; or as having a Body Mass Index (BMI) greater than 30 in men, and 28 in women.
- ◆ Obesity is the major nutritional disorder in the developed world, and carries increased risk of other conditions, e.g. cardiovascular disease, type II diabetes, and cancer.
- ◆ Coronary heart disease is a multi-factorial disease (having many causes) and diet is a major factor.

Gaseous exchange and exercise

Content

- ▼ The gaseous exchange system.
- ▼ The consequences of exercise.

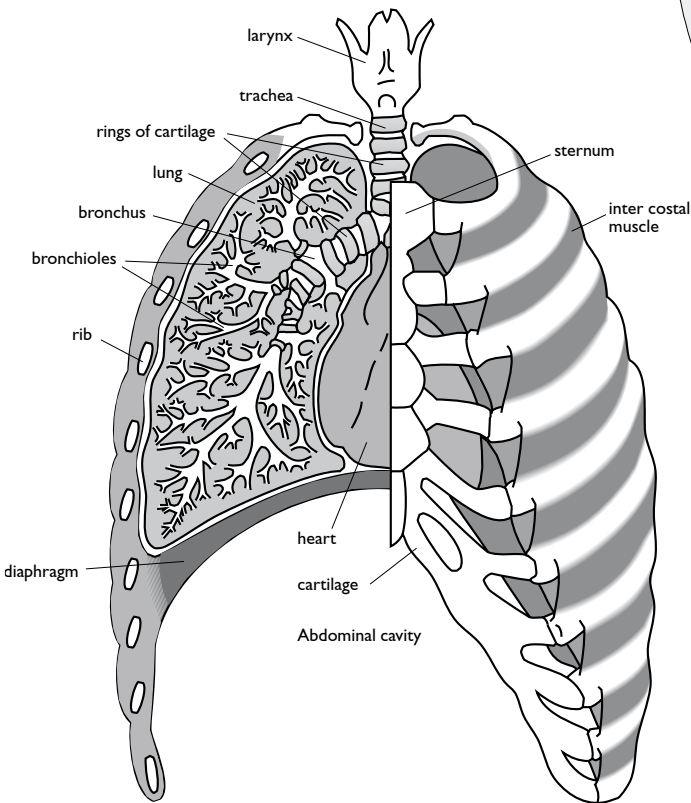
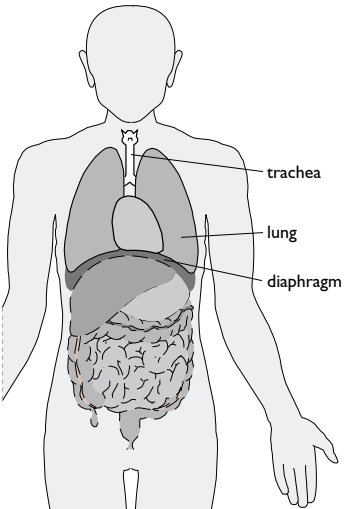
Learning Outcomes

Candidates should be able to:

- a) describe the distribution of alveoli and blood vessels in lung tissue.
 - b) describe the distribution of cartilage, ciliated epithelium, goblet cells and smooth muscle in the trachea, bronchi and bronchioles.
 - c) describe the functions of cartilage, cilia, goblet cells, smooth muscle and elastic fibres in the gaseous exchange system.
 - d) explain the meanings of the terms tidal volume and vital capacity.
 - e) measure the pulse rate and understand that pulse rate is a measure of heart rate.
 - f) explain the significance of resting pulse rate in relation to physical fitness.
 - g) explain the terms systolic blood pressure, diastolic blood pressure and hypertension.
 - h) explain the meaning of the term aerobic exercise.
 - i) describe the immediate effects of exercise on the body, including the concept of oxygen debt and the production of lactate by anaerobic respiration.
 - j) design and carry out experiments to investigate the effects of exercise on the body.
 - k) appreciate how much exercise needs to be taken for significant sustained improvement in aerobic fitness.
 - l) discuss the long term consequences of exercise on the body and the benefits of maintaining a physically fit body, relating these benefits to the concept that health is more than the absence of disease.
-

**STRUCTURE and FUNCTION
of the RESPIRATORY SYSTEM**

One of the most fundamental of the life processes is gaseous exchange. Oxygen must be taken in from the air to the blood where it can be transported around the body to cells where it is used in respiration. At the same time, carbon dioxide, a waste product of respiration must be removed from the blood and released back into the air. This exchange of gases occurs within the alveoli of the lungs but relies on the specialised structure of the respiratory system (trachea, bronchi, bronchioles, alveoli), the breathing movements associated with the ribs and diaphragm, and the cardio-vascular system (heart, blood vessels and blood) to function.



Alveoli

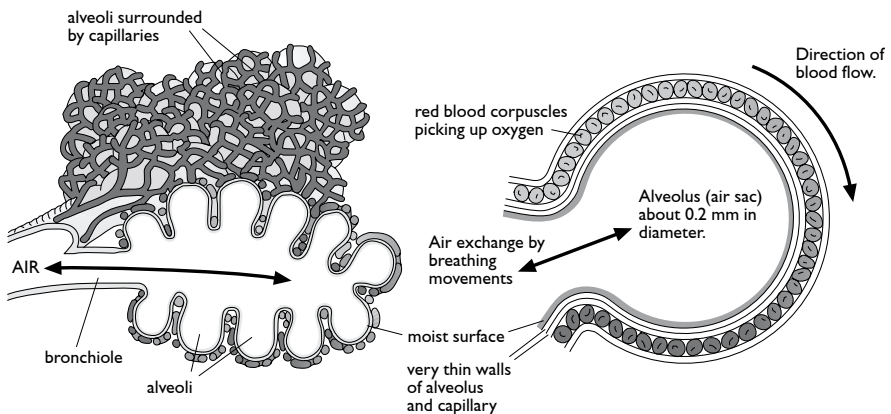
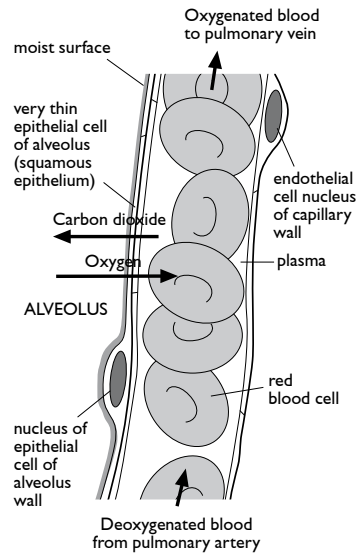
Alveoli or air sacs make up the mass of the lungs. Within the chest cavity the major airway, the **trachea**, branches to form two **bronchi**, which in turn branch to form numerous smaller **bronchioles**. At the ends of the bronchioles the tubes, now only 1-2mm in diameter, become known as alveolar ducts which lead to the alveoli; small chambers used for gas exchange. Alveoli may be arranged along the alveolar duct in a linear fashion or may cluster together around a common opening to the duct. This arrangement is known as an alveolar sac. Although each alveolus is very small, the large numbers of alveoli provide an enormous surface area for gas exchange.

Blood vessels

The blood vessels that supply the alveoli belong to the pulmonary circulation. Whilst other parts of the lung (including the bronchi and pleural membranes) receive blood from the bronchial arteries, it is the pulmonary arteries which supply blood for gaseous exchange. Deoxygenated blood enters the lungs via the pulmonary artery which initially splits into right and left branches and then follows the airways, branching through the tissue of the lungs.

Each alveolus is surrounded by a net of capillaries which together form the **alveolar-capillary complex**. As this name suggests, the endothelium of the capillaries is attached to the thin squamous epithelium of the alveolus via a shared basal membrane. The air inside the alveolus and the blood in the capillaries is thus separated by the thickness of two layers of cells. This is one feature that helps rapid diffusion of oxygen from alveolus to blood and carbon dioxide from blood to alveolus. Other features include the large surface area already mentioned, and the steep diffusion gradients which are maintained between the blood and the alveolus due to the constant movement of the blood and the constant ventilation of the lungs.

Gas exchange alveolus/capillary



STRUCTURE of the TRACHEA, BRONCHI and BRONCHIOLES

Trachea, bronchi and bronchioles form a system of branching air tubes referred to as the 'bronchial tree'. The wall of the trachea and bronchi are composed of four layers. These are the inner mucous membrane or **epithelial** layer, a **submucosa** layer consisting of connective tissue, elastic fibres and mucous glands, a layer of **smooth muscle** and **cartilage**, and a tough outer coat of **connective tissue**. When the the diameter of the bronchioles reaches 1 mm there is no cartilage, and they do not have mucous glands present in the submucosa. In very narrow bronchioles the smooth muscle and elastic fibres may form a single layer.

Cartilage

Cartilage supports the trachea and bronchi and prevents their collapse. In the trachea the cartilage forms C-shaped rings which are arranged so that the open ends of the C are at the back of the tube, facing towards the spine. These support the tube and keep it open during inspiration expiration (breathing in and out). The incomplete nature of these 'rings' of cartilage allows a degree of compression due to the expansion of the oesophagus when swallowing food. In the bronchi the cartilage does not form rings but instead forms plates.

Smooth muscle

Involuntary (smooth) muscle found in the trachea, bronchi and bronchioles can regulate the diameter of the tubes. In conditions like asthma and anaphylaxis, where constriction of the bronchioles occurs restricting air flow.

Epithelium

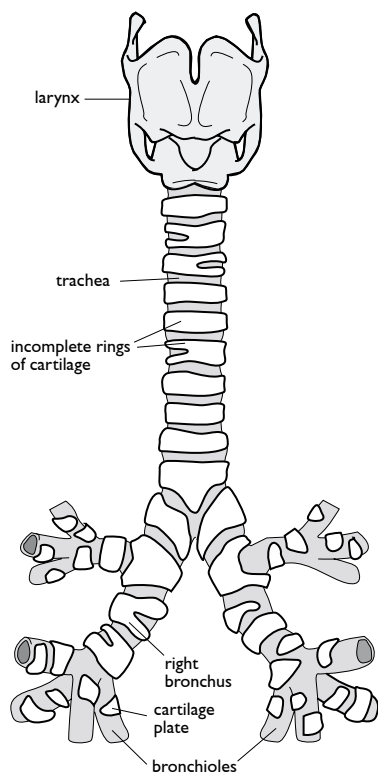
The epithelium lining the trachea, bronchi and bronchioles is known as the mucous membrane, and consists of ciliated columnar epithelium. This possesses three main cell types: ciliated cells, goblet cells and basal cells. At the very end of the bronchioles, close to the alveoli (the terminal and respiratory bronchioles) no goblet cells are found, only ciliated cells.

Ciliated epithelial cells have a protective function as they work in a co-ordinated fashion sweeping the mucus coat of the air passages which contains small inhaled particles such as dust towards the pharynx (throat and mouth) where they can be swallowed or removed by the cough reflex. This prevents such particles form entering the alveoli and interfering with gaseous exchange.

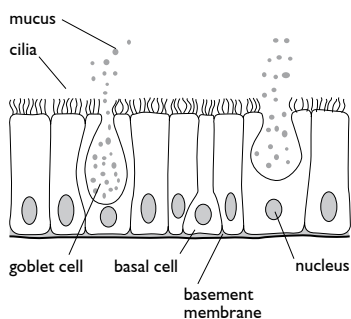
Goblet cells which are interspersed amongst the ciliated cells in the trachea and bronchi, are responsible for producing and secreting mucus within the respiratory tract. The layer of mucus which lines the airways traps dust and bacteria. It may also play a role in humidifying inhaled air.

Elastic fibres

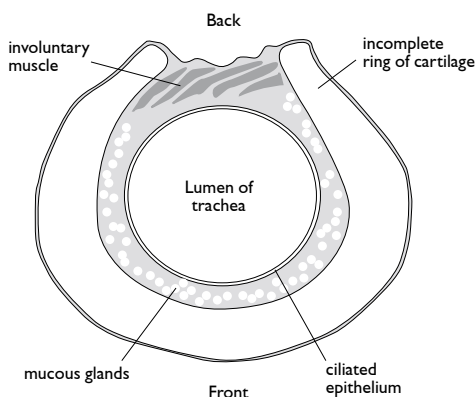
Elastic fibres confer elasticity upon the tissues, allowing contraction back to the original form after stretching.



Respiratory ciliated columnar epithelium



Section through trachea showing cartilage



◆ CHECKPOINT SUMMARY

- ◆ The lungs have a huge internal surface area as a result of the millions of air sacs (alveoli).
- ◆ The pulmonary arteries supply the lungs from the right atrium, and the pulmonary veins return oxygenated blood to the left atrium of the heart.
- ◆ The pulmonary capillary beds supplying the alveoli are amongst the densest in the body.
- ◆ The lungs are organs composed of several specialised tissues.
- ◆ Cartilage supports the larger airways preventing collapse when the internal pressure of the thorax is reduced.
- ◆ Goblet cells secrete mucus which traps inhaled particles, and cilia sweep it up the trachea to be removed by the cough reflex.
- ◆ Smooth muscle fibres can alter the diameter of the airways by its contraction and relaxation.
- ◆ Elastic fibres enable the lung tissues to accommodate the changes in volume involved in breathing in and out, and enables breathing out to be passive by elastic recoil of the stretched tissues

BREATHING and LUNG VOLUMES

For efficient gaseous exchange at the alveolar surface, air must be moved in and out of the lungs. This is achieved by the breathing movements of the intercostal muscles of the ribs, and the muscular diaphragm both of which are controlled by the autonomic and voluntary nervous systems.

During **inspiration** (breathing in) the external intercostal muscles contract pulling the ribs upwards and outwards. At the same time the diaphragm contracts, moving downwards. Both movements increase the volume of the thorax, reducing the pressure in the thorax below atmospheric pressure causing air to enter, inflating the lungs. At rest **expiration** (breathing out) does not involve active muscle contractions, but depends upon the elasticity of the tissues of the lungs and thorax.. The external intercostal muscles relax, allowing the rib cage to move downwards and inwards, and the diaphragm relaxes and regains its domed shape. The volume of the thorax is reduced, pressure increased and air forced out of the lungs. During forced breathing, for example as a result of exercise or in speech, expiration is active, with the internal intercostal muscles and abdominal muscles contracting to increase the pressure within the thorax.

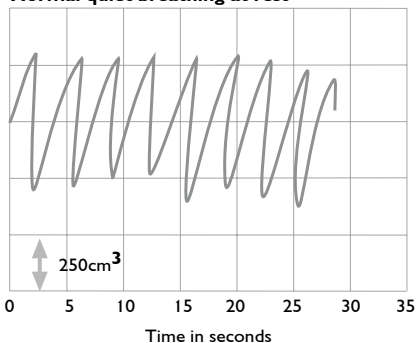
Friction between the lungs and the inner surface of the wall of the thorax is reduced by the **pleural fluid** which lies between the two pleural membranes that surround the lungs.

Breathing movements thus result in certain volumes of air passing into and out of the lungs.

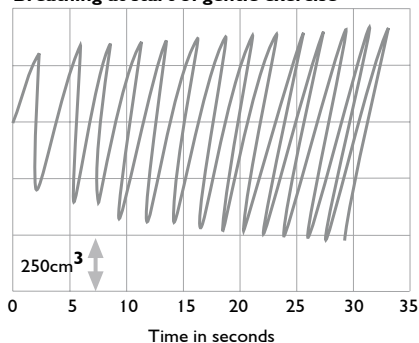
Tidal volume

This is the volume of air breathed in and out in a single breath in a single breathing cycle. During normal quiet breathing at rest, a healthy, active mature male of average height would have a tidal volume of about 500 cm^3 . Of this 500 cm^3 , about 350 cm^3 reaches the alveoli where gaseous exchange occurs. The remaining 150 cm^3 fills the pharynx, larynx, trachea, bronchi, and bronchioles, which compared to the alveoli are poorly supplied with blood capillaries, so that very little, if any, gaseous exchange occurs here. This space where no gaseous exchange occurs is known as the anatomical **dead space**, and the air that occupies it as the **dead air volume**.

Normal quiet breathing at rest



Breathing at start of gentle exercise



The 350 cm^3 of the tidal volume that reaches the alveoli, mixes with the 150 cm^3 of air remaining in the dead space from the previous exhalation, so that 500 cm^3 of mixed air reaches the alveoli on each inspiration. Here it mixes with the air that remains in the alveoli in quiet breathing, the **stationary air volume**, which can be up to 2500 cm^3 . Thus the alveolar air consists of about 350 cm^3 of fresh air mixed with up to 2500 cm^3 of air that has undergone gaseous exchange with the blood, and 150 cm^3 of previous dead space air. Therefore the composition of alveolar air does not fluctuate widely during the breathing cycle, which in turn ensures that gaseous exchange with the blood also remains fairly constant throughout the breathing cycle. However, when the tidal volume increases during exercise, more 'fresh air' does reach the alveoli.

By breathing in as deeply as possible an extra volume of air, in addition to the tidal volume and the stationary air, can be taken into the lungs. This is the **inspiratory reserve volume** and can be up to 2000 cm^3 . By breathing out as forcibly as possible after returning to normal breathing, it is possible to expel some of the stationary air in addition to the tidal volume. This is known as the **expiratory reserve volume** and can be up to 1500 cm^3 . However the lungs cannot be emptied entirely, otherwise they would collapse, and this remaining air is known as the **residual volume** which can be up to 1500 cm^3 .

◆ CHECKPOINT SUMMARY

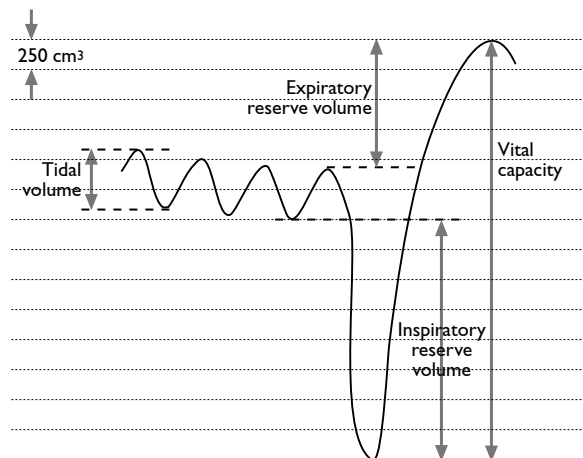
- ◆ Tidal volume is the volume of air breathed-in and out during a single breathing cycle.
- ◆ The tidal volume increases with aerobic exercise.
- ◆ The mixing of air in the alveoli results in a fairly constant level of oxygen in the alveoli, irrespective of the point of the breathing cycle.
- ◆ The vital capacity is the greatest volume of air that can be moved in and out of the lungs in one breathing cycle.
- ◆ The tidal volume cannot approach the vital capacity as it is not possible to move such volumes of air over the lungs during rapid breathing.
- ◆ Lung volumes are closely correlated with height.

Vital capacity

This is the sum of the inspiratory reserve volume, the tidal volume, and the expiratory reserve volume. The vital capacity represents the maximum total amount of air that can be moved into and out of the lungs by one inhalation and one exhalation, and is about 3000 cm^3 - 4000 cm^3 in the adult male.

These volumes and the lung capacities vary considerably between individuals. They are generally smaller in females than in males, due to smaller average body size in females, and correlate closely with body size, height and surface area up to age 25. As discussed in section 5.2.4, smoking and associated lung diseases can considerably reduce lung volumes and capacities.

Vital capacity trace



This trace does not show the total lung volume and residual volume, which are not easily measured. With increasing age the residual volume increases from about 20% of the total lung volume to more than 30%.

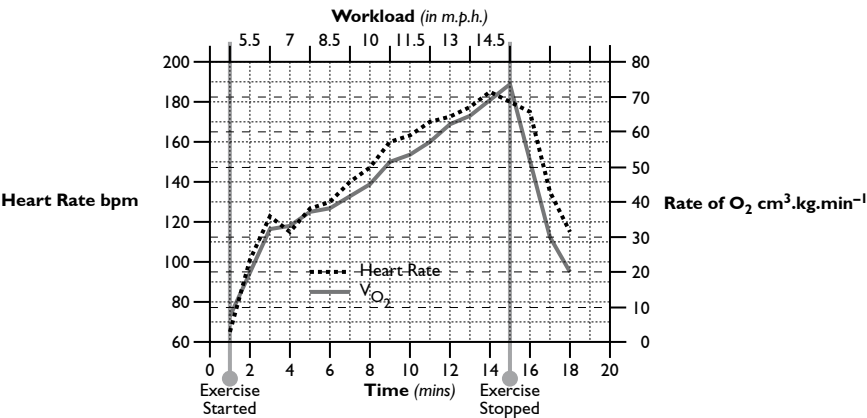
HEART RATE and PULSE RATE

The mammalian heart works as a four chambered pump. The left atrium of the heart receives blood high in oxygen from the lungs and passes it to the left ventricle which pumps it around the body. Amongst other functions this supplies cells with oxygen and glucose for respiration. The right atrium of the heart receives blood low in oxygen from cells of the body and passes it to the right ventricle. It is then pumped to the lungs to collect oxygen and release carbon dioxide. A single heart beat represents the stages from filling of the atria to contraction of the ventricles which occur simultaneously on both sides.

As the ventricles of the heart contract, blood is forced into the main arteries leaving the heart, the aorta and the pulmonary artery. Blood enters the aorta at very high pressure and the thick elastic wall of the vessel is momentarily stretched as the blood enters. It then recoils as the blood moves on (causing stretching in the next section of artery). This recoil assists the circulation of the blood around the body, helps smooth the flow between contractions of the heart, and helps to maintain the blood pressure. This wave of stretching and recoiling in the walls of the arteries can be felt as the pulse in places where arteries come close to the surface of the body (the inside of the wrist, the side of the neck, and in the temple). The pulse thus reflects the rate of the heart beat and is the most common means of measuring heart rate. The pulse gradually fades as the arteries branch into the arterioles.

As the heart rate rises during exercise, owing to increased demand for oxygen and glucose by muscles, so does the pulse rate. A resting pulse rate (heart rate) of around 70 beats per minute can increase to over 200 during vigorous exercise. The maximum heart rate decreases with age, so that an estimate of your maximum heart rate can be given by the result of 220 minus your age.

Heart rate and oxygen uptake in response to exercise



The heart rate of individuals doing the same exercise may, however, vary considerably. Heart size varies between people, being usually though not always correlated with body size. In general the larger the heart the slower the maximum heart rate, as it takes longer for a larger heart to fill with blood between contractions. It is important to note that this is usually regarded as being beneficial since the rate at which blood is pumped into arteries and hence to tissues (the cardiac output), depends not only on the heart rate, but also on the amount of blood pumped out of the ventricles at each contraction (the **stroke volume**). The stroke volume is determined by the extent to which the ventricles fill with blood and by the force of contraction of the ventricles. These two factors are inter-related, the fuller the ventricles, the greater the force of contraction. Cardiac output is therefore equal to heart rate x stroke volume. Endurance training over long periods of time can lead to the enlargement of the heart - a condition known as athlete's heart.

THE SIGNIFICANCE of RESTING PULSE RATE in RELATION to PHYSICAL FITNESS

The **resting pulse** is defined as the pulse rate measured when an individual is at complete rest. It is usually taken when an individual is lying down first thing in the morning. It represents the response of the heart to basic metabolic demands of the body at rest (mental and physical). In general the larger and more powerful the heart of an individual (perhaps as a result of endurance athletic training) the lower will be the resting heart rate. This is because more blood will be pumped out of their ventricles on each contraction (the stroke volume is larger). Thus for a given cardiac output the heart rate is reduced, with some highly trained endurance athletes having resting pulse rates as low as 30 beats per minute.

It can therefore be said that as physical fitness (of the endurance type) increases, heart rate decreases, both at rest and during exercise of a given intensity. This is beneficial as it means that the heart is working less hard and has a lower oxygen demand. Another measure of fitness is the rate at which the heart rate returns to its resting rate after a set period of exercise at a given intensity, the faster the return to normal the greater the physical fitness.

BLOOD PRESSURE

The heart pumps blood around a complete circuit of vessels, which offer resistance to the flow of blood, therefore pressures are generated within the system. Blood pressure is usually measured in the brachial artery in the left arm using a sphygmomanometer. It is measured clinically in mm of mercury (mm Hg). As a result of the action of the heart there are two measures of blood pressure.

Systolic blood pressure

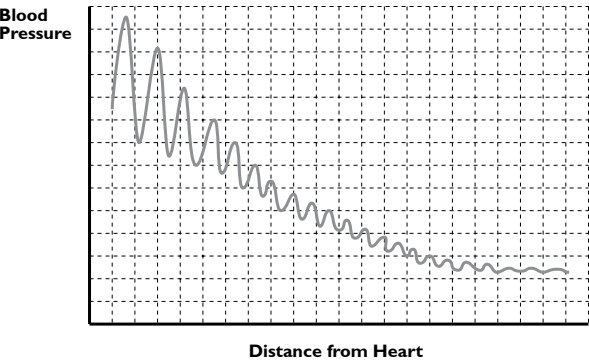
Systolic blood pressure is that pressure generated when the ventricles are contracting (about 120 mm Hg in a young healthy adult). A rough estimation of systolic blood pressure can be derived from adding 100 to your age.

Diastolic blood pressure

Diastolic blood pressure is that pressure when the ventricles are relaxing (about 80 mm Hg in a young healthy adult). With regard to checking blood pressure, the diastolic pressure gives the clearest indication of the state of the resistance offered to flow by the blood vessels (peripheral resistance), as the heart is not contracting at this time.

Blood pressure is expressed as a ratio of systolic to diastolic blood pressure e.g. 120/80 mm Hg.

The average of the systolic and diastolic pressures during a complete cardiac cycle, known as the mean blood pressure, determines the overall rate of blood flow through the circulation. The blood pressure drops as the blood gets further away from the left ventricle and circulates around the body. Some typical figures for the mean blood pressure (in mm Hg) whilst at rest are: arteries 100, capillaries 18, veins 7, and at the entrance to the right atrium 3.



Blood pressure is generated by the cardiac output (heart rate x stroke volume) and the resistance to flow of the blood in the blood vessels. The resistance is often referred to as the peripheral resistance, as the major part of it occurs in the smaller vessels (mainly the arterioles) at a distance from the heart. The resistance

to flow is due to the friction between the blood and the walls of the blood vessels. The friction is determined by the length, diameter, and the smoothness of the lining of the vessels, and the viscosity of the blood. The shorter the vessel, the larger the diameter and the less viscous the blood, the lower the resistance. These features, particularly vessel diameter, are not fixed in an individual but change according to circumstances. Both acute (short term) and chronic (long term) changes can occur.

Arteries and arterioles (and to a lesser extent veins and venules) have involuntary muscle fibres in their walls, which when contracted constrict the vessel reducing its diameter. This can lead to short-term (acute) rises in blood pressure which occur at times of emotional stress, or following intake of certain drugs including nicotine. The systolic and diastolic blood pressures are also raised considerably during static (isometric), straining type exercises, as in weight training. This is caused by compression of the peripheral blood vessels, causing an increase in the resistance to blood flow and a demand for increased blood pressure, to maintain the circulation to the contracted muscles. Acute increases in blood viscosity, which lead to increased resistance and increased blood pressure can occur during periods of dehydration due to excess water loss in sweating, or in the urine following consumption of substances that increase urine production (diuretics) such as alcohol and caffeine.

Hypertension

Hypertension is chronic high blood pressure as a result of permanently high peripheral resistance. There is no universally agreed clinical definition of hypertension nor any reliable signs and symptoms, but a systolic blood pressure over 160mm Hg and diastolic blood pressure over 95mm Hg on several consecutive readings would lead to a definite diagnosis of this condition. Pressures of 140/90 mm Hg may be borderline (compared to average values of 120/80 mm Hg in a healthy young person.) There is, however, much natural variation in blood pressure between individuals, making diagnosis more difficult

Whilst hypertension is one of the most common disorders in the developed world, particularly amongst older people, in most cases there is not a single causative factor. It is thought to be linked to activity of the sympathetic nervous system causing excessive vasoconstriction and to disturbance in the salt and water balance of the body. Suggested causes are high salt diets and obesity. Smoking-related lung disorders (see section 5.2.4) can lead to pulmonary hypertension. The consequences of hypertension include having increased risk of developing atherosclerosis, cerebral haemorrhage and kidney failure.

Regular aerobic exercise over a period of time can result in a lowering of the resting systolic and diastolic blood pressures. Exercise of this type decreases the peripheral resistance as the circulation becomes more efficient, increases the ratio of the high density to low density lipoproteins in the blood, and together with the appropriate diet aids weight loss.

◆ CHECKPOINT SUMMARY

- ◆ The surge of blood pumped out of the heart into the arterial system and the subsequent recoil of the arterial walls when the heart relaxes is felt as the pulse.
- ◆ The pulse rate is thus determined by the heart rate.
- ◆ The resting pulse rate is a measure of physical fitness. At rest, the metabolic demands of similar individuals are approximately the same, and are met by the cardiac output.
- ◆ The cardiac output is the product of the heart rate and the stroke volume.
- ◆ The individual with the lower resting pulse rate is meeting those demands with the same cardiac output, and must therefore have a higher stroke volume. Stroke volume is proportional to the size and power of contraction of the heart. A large powerful heart is a major component of aerobic physical fitness.
- ◆ When the ventricles contract (ventricular systole) the systolic blood pressure is generated as a result of the resistance to flow within the arterioles.
- ◆ When the ventricles relax (ventricular diastole) the pressure in the arterial system drops and is known as the diastolic blood pressure.
- ◆ These pressure changes are felt in the pulse.
- ◆ A complex of factors including a loss of elasticity in the walls of the arterial system with age, narrowing of arteries by fatty deposits, and increased blood volume, lead to increased resistance to flow and hence higher blood pressure or hypertension.
- ◆ Short term (acute) rises in blood pressure can occur in response to specific situations as a result of anxiety, such as 'white coat hypertension' when people enter a medical environment.
- ◆ Long term (chronic) rises in blood pressure (essential hypertension), especially diastolic blood pressure, indicate a permanent rise in resistance to flow in the arterial system.
- ◆ Hypertension carries risks, particularly to the kidneys, and the brain where ruptured blood vessels result in 'strokes'.

AEROBIC EXERCISE

Exercise can be basically divided into two types. **Aerobic exercise**, for example jogging, where oxygen supply to the muscles meets the oxygen demand of the muscles for the release of energy by aerobic respiration; and **anaerobic exercise** where oxygen supply to the muscles does not meet the oxygen demand of the muscles for aerobic respiration (anaerobic means 'without oxygen'). Both systems may operate together, but typically one predominates in a particular type of exercise. Many sports and games which require sudden bursts of effort such as football, combine periods of both aerobic and anaerobic exercise.

Aerobic exercise enables sufficient oxygen to be delivered to working muscles by the blood, and as a result carbohydrates and fats inside cells can undergo complete oxidation, being converted into carbon dioxide and water, with the release of energy in the form of ATP. It occurs in cells whilst the body is at rest and during endurance type sports. The following equation can be given for aerobic respiration:

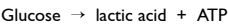


Aerobic respiration take place in three main stages. The first, **glycolysis**, occurs in the cytoplasm of cells, does not involve oxygen directly and releases a small amount of ATP very rapidly. The second, which releases most of the energy, occurs in the matrix of the mitochondria, and the third in which the energy is trapped as ATP on the inner membranes (cristae) of the mitochondria. In this way molecules of ATP are released from the complete oxidation of one molecule of glucose.

Aerobic exercise, unlike anaerobic exercise, can be maintained over long periods of time (many hours or even days) as long as there are sufficient fuel supplies. The increased production of carbon dioxide which occurs has a direct effect on the cardiac and respiratory control centres in the brain. In lowering blood pH it stimulates an increase in the cardiac output (increase in heart rate and stroke volume) and an increase in the rate and depth of breathing which adapt to the level of exercise being undertaken. Marathon running and swimming the Channel are good examples of aerobic exercise lasting several hours.

ANAEROBIC EXERCISE

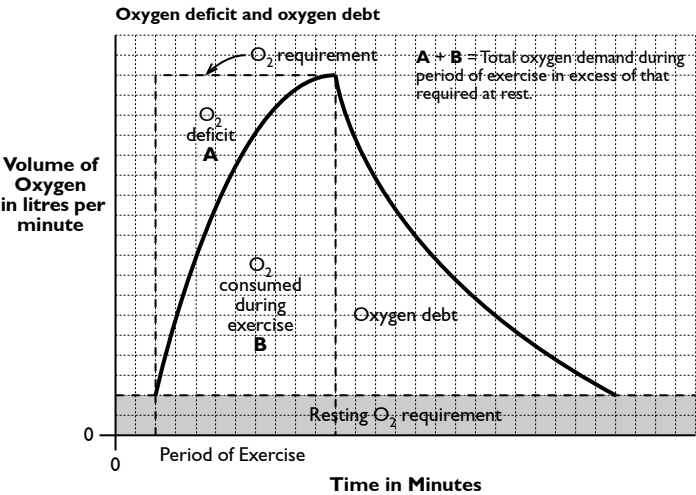
Whenever the demand for oxygen during exercise is greater than its supply, the muscle fibres are forced to release energy from their energy stores anaerobically, without oxygen. This can occur at the onset of vigorous activity, or at any time during exercise when the effort is increased above a certain level, and when the heart and circulation have not had time to adapt to the increase in demand. In the absence of oxygen the breakdown of glucose is incomplete, with the production of lactic acid and the rapid release of relatively small amounts of energy (2 molecules of ATP per molecule of glucose: only 5% of what can be released aerobically). The equation for anaerobic respiration, which occurs in the cytoplasm of muscle fibres is:



Note that under the conditions existing inside the body the lactic acid dissociates to form hydrogen ions and lactate ions, so it is preferable to refer to **lactate** rather than lactic acid (which remains in common usage).

A small amount of lactate is formed even during the lightest exercise as not all muscle fibres will be sufficiently supplied with oxygen, especially at the start of exercise. However, if its rate of removal is more than or equal to its rate of production, it does not accumulate in the muscles or the blood. It is transported in the blood to organs which are not operating under anaerobic conditions, such as the heart, brain and liver, where it can be oxidised. When the rate of production does exceed its rate of removal, lactate begins to accumulate in the muscles and the blood. The resulting reduced blood pH (increased acidity) increases fatigue, and increases the rate of breathing, eventually past even the point at which any extra oxygen uptake can be achieved. It is around the start of this process of lactate accumulation during exercise that conversations tend to stop! Past a certain upper limit the anaerobic respiration will cause enough distress to force the activity to stop.

Oxygen debt is a concept relating to the fact that whilst exercising anaerobically the body can be considered to be short of a certain amount of oxygen (the **oxygen deficit**) and that after exercise, breathing and cardiac output remain high for a period of time to supply an amount of oxygen equivalent to that amount undersupplied during exercise. Originally the extra amount of oxygen required during recovery, was assumed to be just that which was needed for the removal of the accumulated lactate (by aerobic respiration to carbon dioxide and water, yielding ATP) and was therefore referred to as the 'oxygen debt'. However, there is only a slight relationship between the oxygen deficit and the so-called 'oxygen debt'; with the 'oxygen debt' being up to twice the oxygen deficit. Therefore the 'oxygen debt' is not simply involved with the repayment of a deficit incurred during exercise. It also compensates for the extra oxygen needed after the period of anaerobic exercise,



including that needed to supply the muscles of the thorax responsible for the increased breathing rate, and the more rapid beating of the heart. Also the oxygen required to maintain the higher metabolic rate due to the raised body temperature, and the residual effects of the hormones adrenaline and thyroxine. The redistribution of ions (such as calcium, potassium and sodium) in the fluids inside and outside of cells after exercise, also requires energy and therefore oxygen. In recovery from strenuous exercise, which has resulted in the production of lactate, it may be as long as 24 hours after stopping exercise before the oxygen consumption returns to pre-exercise levels.

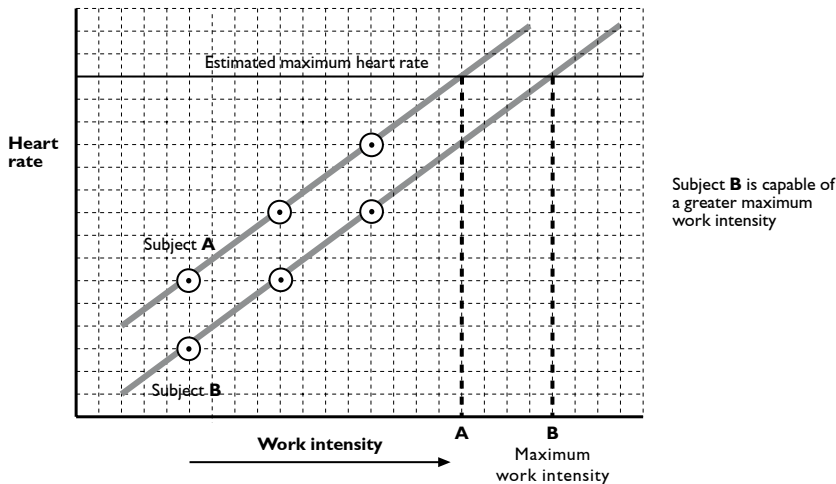
EXPERIMENTAL INVESTIGATION of the EFFECTS of EXERCISE on the BODY

Experimental investigations into the effects of exercise can be performed during sub-maximal or maximal exercise. In **sub-maximal exercise**, measurements are taken in a zone of exercise intensity that the subject finds comfortable, and from these it is possible to project trends to determine maximum values of, for example, work intensity or oxygen uptake. Such projections depend on various assumptions. One assumption is that there is a straight line relationship between the two measurements being taken, e.g. heart rate and exercise intensity, and heart rate and oxygen uptake. In other words as the independent variable increases (e.g. exercise intensity) the dependent variable (e.g heart rate increases proportionally). Another assumption is that the maximum heart rate can be estimated accurately by means of the formula: maximum heart rate = 220 minus the age of the subject. For example in the case of a 20 year old this would give a maximum heart rate of 200 beats per minute. Thus if a subject is exercising at three sub-maximal work intensities, and three heart rates are measured at

CHECKPOINT SUMMARY

- ◆ Aerobic exercise is at that intensity at which the demand for oxygen by the active muscles can be met by the supply of oxygen in the blood.
- ◆ Aerobic exercise is characterised by relatively low intensity for relatively long periods, during which the body is in a 'steady state', and conversation is possible.
- ◆ Anaerobic respiration occurs when the demand for oxygen by the tissues is not met by the supply of oxygen in the blood.
- ◆ Anaerobic respiration results in the rapid release of relatively small amounts of oxygen and the production of lactate as a by-product.
- ◆ When the intensity of exercise eases, and/or the circulatory and respiratory systems have adjusted to supply the demand for oxygen by the working muscles, the accumulated lactate is oxidised.
- ◆ The oxidation of the accumulated lactate uses a volume of oxygen equivalent to the amount that the body was short of during the anaerobic exercise.
- ◆ In this way the 'oxygen debt' is paid off.
- ◆ The excess post-exercise oxygen consumption (EPOC) is greater than the 'oxygen debt' as there are many post-exercise processes which demand extra oxygen until the metabolism returns to its resting levels.

Projections from sub-maximal work



these intensities, then a line can be drawn and extended to the calculated maximum heart rate, and an estimate of the maximum work intensity be obtained. Estimating the maximum heart rate by using the formula 'maximum heart rate = 220 minus the age of the subject' is not very accurate, as everybody varies slightly and endurance trained athletes can develop a larger heart and thus a lower maximum heart rate. In these cases the maximum work intensity would be overestimated by using the formula.

Despite these inaccuracies sub-maximal tests have the advantage over maximal tests in that they avoid the question of motivation (whether the subject really was exercising maximally). Also the subject is not unduly stressed, which could be dangerous if the subject has any condition made worse by intense effort, such as certain heart conditions.

Methods of controlling and measuring work intensity are required for all tests of the effects of exercise on the body, and these include the simple step test, treadmill, and cycle ergometer.

Fitness is very specific, and usually runners perform better on the treadmill, and cyclists on the cycle ergometer. The step test is more 'event neutral', but even here differences in height and coordination will affect the outcome.

EXERCISE and AEROBIC FITNESS

Defining and measuring fitness is difficult, but fitness can be thought of as the capacity to perform repeated physical activity with relative success and enjoyment. With some strenuous sports, the exertion is so great that it could hardly be considered enjoyable at the time, however in these cases the enjoyment derives from the sense of achievement that follows the exertion. Any discomfort experienced is generally soon forgotten as a result of the body's rapid recovery. Indeed a common measure of fitness is the speed of recovery after exertion. In less physically demanding skill-based sports, physical fitness can be considered as that state which prevents fatigue from interfering with the performance of the skill.

Perhaps the clearest definition of physical fitness would be to relate it to the ability of the body to respond to the physical demands made upon it by improving its capacities, that is a person responds to physical demand by becoming 'fitter'. This is the main principle of training practices, namely progressive overload with adequate recovery leading to adaptation. A battery of tests exists for investigating various anatomical and physiological systems, and the results of these tests can in turn be used to define various levels and categories of 'fitness'.

Significant sustained improvement in aerobic fitness can be achieved by raising the pulse rate in steady state aerobic exercise up to the point of conversation becoming difficult (if running in company) for about three 30 minute sessions a week. Gains made in aerobic fitness only persist if the exercise is maintained. Should the exercise be stopped for some reason, gains in fitness are lost. The rate of loss is approximately three times more quickly than the rate of gain.

**LONG TERM CONSEQUENCES of EXERCISE:
FITNESS and HEALTH**

Exercise has long been recognised as an important component of the physical health of individuals, and has been incorporated into formal education programmes in schools for well over a century. More recently it has been recognised that exercise can help to reduce the risk of illness or death from some of the degenerative diseases which are becoming increasingly common across the world. Exercise is thus promoted as a preventative measure in a range of diseases. It has also been suggested that exercise may benefit the mental well-being of individuals, leading to overall improvements in health (see section 5.2.1 for definition of health).

Components or dimensions of physical fitness relating both to sport performance and general health include:

Cardio-Respiratory endurance - the capacity/ability to sustain aerobic work.

Muscular endurance - the ability to sustain local muscle action.

Strength - that force exerted by muscles in a single maximal contraction.

Mobility/Flexibility - the range of movement about the joints.

Body composition - the relative amount of body fat compared to lean body mass.

Speed - the quickness of action of either whole body or part body movements.

Power - the work performed in a given time, a combination of strength and speed.

Agility - the ability to alter the position of the body and/or its parts, quickly, and accurately in a controlled manner.

Balance - the ability to control the position of the centre of gravity/mass and maintain it within and above the area of the base of support.

Co-ordination - the ability to combine the action of various parts of the body in a controlled manner.

Health benefits of exercise are not easily demonstrable, but there is an accumulation of reliable scientific evidence that sustained (regular) aerobic exercise of the correct type promotes what is generally understood as good health, both physical and mental, in young and old alike. It may play a significant role in preventing early death but does not necessarily increase longevity above average. Individuals should thus aim to make regular exercise a part of their lifestyle, even if this exercise is only walking and climbing the stairs instead of using cars and escalators. There is no universally agreed level of exercise above which health benefits may be felt, but with the increasingly sedentary lifestyles of western populations any increase in exercise is likely to be beneficial.

The most widely appreciated of these benefits relate to the effects of exercise on the cardiovascular system. These effects, many of which overlap, can be summarised as follows:

- ▼ Reduction in or prevention of obesity through increased utilisation of body fat.
- ▼ Reduction in risk of hypertension through a decrease in the peripheral resistance

- ▼ Reduction in ratio of harmful LDLs (cholesterol) to protective HDLs in the blood
- ▼ Reduction in the risk of Type II diabetes (late onset type) through maintaining the sensitivity of the tissues to insulin
- ▼ Reduction in risk of coronary thrombosis through increased blood flow through the coronary arteries and increased fibrinolytic activity (breakdown of clots) within the blood.
- ▼ Lowering of average heart rate during sub-maximal exercise and at rest, so reducing the demands on the heart.
- ▼ Improvement in the stability of the electrical activity of the heart, which decreases the risk of life threatening disturbances in their pattern (as seen in the ECG trace).
- ▼ Reduction in stress through aiding relaxation and improving the quality of sleep.

In summary, vigorous aerobic exercise at least three times a week reduces the risk of a myocardial infarction (heart attack) by at least 50%.

In addition to these benefits on cardio-vascular health, exercise of all types has a beneficial effect on the musculo-skeletal system. Muscles, tendons, ligaments and bones all weaken as a result of disuse. During prolonged inactivity up to a third of the calcium salts, which are responsible for the hardness of bone, can be lost in a process of demineralisation, leading to the weakening of the bone known as osteoporosis and increased risk of fractures. Exercise protects against this bone loss, and can more than compensate for the loss of bone mass that occurs in post-menopausal women. Exercise can also increase the tensile strength of tendons and ligaments, and as a result of the release of growth hormone stimulates the synthesis of tissue protein especially in the muscles.

Other effects of exercise which are often quoted although difficult to prove scientifically, include improved appearance, improved confidence about one's body, improved quality of skin and hair, improvements in mood and improved sociability. If such effects are real phenomena, mediated by physical or mental changes in the body, then it is likely that they will contribute significantly to overall health, including the social and mental dimensions of health. Such benefits are however, only maintained if the exercise is sustained.

All these benefits of maintaining a physically fit body illustrate the concept that health is more than the absence of disease.

Whilst many aspects of exercise are positive, and regular carefully graded aerobic exercise in itself carries very little risk, there can be negative effects. Over-exertion and over-training in some individuals can lead to extreme tiredness and excess weight loss perhaps in association with some eating disorders. In addition the activity of the immune system may be depressed for a period of up to 24 hours after exhaustive exercise, opening the way for infection. Care should also be taken to avoid over-exertion whilst infected, as this may be a factor in the development of long term (chronic) conditions such as 'glandular fever', post-viral fatigue syndrome, M.E. (Myalgic Encephalomyelitis), or even some forms of heart disease (myocarditis). There is also the possibility of overuse injuries to the musculo-skeletal system such as pulled muscles, back problems, and stress fractures of bones. In extreme cases over-vigorous anaerobic exercise in untrained individuals at risk of CHD can lead to death from myocardial infarction.

◆ CHECKPOINT SUMMARY

- ◆ Exercise experiments can be maximal or sub-maximal.
- ◆ Sub-maximal exercise experiments are safer and easier to control than maximal exercise experiments.
- ◆ Standardised exercise protocols are necessary, e.g. step test, cycle ergometer, and treadmill.
- ◆ Aerobic fitness can be improved by a simple regime of 30 minutes of steady exercise three times a week.
- ◆ Gains in aerobic fitness are lost three times more quickly than they were achieved.
- ◆ Exercise has long term benefits for health, including reduced risk of cardiovascular disease, type II diabetes, hypertension, obesity etc.
- ◆ The improved statistics associated with aerobic exercise persist only for as long as the exercise is maintained.

Smoking and disease

Content

- ▼ Effects of smoking and disease on the gaseous exchange and cardiovascular systems.
- ▼ Prevention and cure.

Learning Outcomes

Candidates should be able to:

- a) describe the effects of tar and carcinogens in tobacco smoke on the gaseous exchange system
- b) describe the symptoms of chronic bronchitis and emphysema (chronic obstructive pulmonary disease) and lung cancer.
- c) evaluate the epidemiological and experimental evidence linking cigarette smoking to disease and early death.
- d) describe the effects of nicotine and carbon monoxide in tobacco smoke on the cardio-vascular system with reference to atherosclerosis, coronary heart disease (CHD) and strokes.
- e) discuss the reasons for the global distribution of CHD.
- f) discuss the difficulty in achieving a balance between prevention and cure, with reference to CHD, coronary by-pass surgery and heart transplant surgery.

SMOKING and DISEASE

As discussed previously, the main causes of ill health and premature death in the developed world, and indeed in some cities within the developing world, are the non-infectious diseases. Often known as diseases of urbanisation, diseases of affluence or degenerative diseases, these include cancers, cardio-vascular diseases, obesity, diabetes and a range of mental disorders and addictions. As well as being associated with older age, many of these diseases have links with high fat, high calorie and low fibre diets, lack of exercise, mental stress, high alcohol intake and excessive smoking.

Many of these factors interact with each other making the effects of each difficult to distinguish, but smoking tobacco is known to be the largest single cause of preventable death and ill health in Britain. The strong links between smoking and lung cancer, chronic bronchitis, emphysema, and cardio-vascular disease are well established. Similarly, it is associated with increased risk of a range of other types of cancer and other respiratory diseases.

Today around 6-700 billion cigarettes are produced world-wide each year and in excess of 4 million deaths result from their use. World Health Organisation (WHO) predictions suggest that this will rise to 10 million in 2010. Whilst some developed countries now show a slight decline in smoking, (perhaps as a result of increasing cost, changing social customs, public health warnings and increasing health education) the number of smokers in developing countries continues to increase.

EFFECTS of TOBACCO SMOKING
on the RESPIRATORY SYSTEM

Tobacco smoke contains a mixture of many substances including irritant carbon particles, droplets of **tar**, the addictive chemical **nicotine** and a mixture of hot gases including the poisonous **carbon monoxide**. Of more than 1000 components identified more than 17 are known to be carcinogenic (cancer-causing). Many others are harmful in different ways, as demonstrated in studies on animals and observations in humans.

The effects of tar and other carcinogens in tobacco smoke on the gaseous exchange system are numerous. As discussed previously, efficient gaseous exchange relies on respiratory surfaces in the lungs having a large surface area, a short distance over which diffusion must occur, an effective ventilation mechanism and a good blood supply to deliver oxygen and remove carbon dioxide. It also relies on a network of airways to deliver air to these respiratory surfaces and mechanisms to limit the chance of dust or micro-organisms entering the lungs. Smoking can decrease the efficiency of all of these features in the following ways:

- ▼ Carbon monoxide binds to haemoglobin in red blood cells reducing the oxygen carrying capacity of the blood.
- ▼ Collection of tar on the alveolar surface increases the diffusion distance for gaseous exchange.
- ▼ Tar and other substances inactivate cilia and prevent them from clearing respiratory passages of dust and micro-organisms which can reach the alveoli leading to irritation and increased risk of infection.
- ▼ Inflammation of the bronchioles by tar and smoke causes constriction and secretion of fluid and mucus allowing less air into and out of the lungs (Bronchitis). Smoking may also make asthma worse.
- ▼ Nicotine may also cause constriction of bronchioles as a result of stimulating contraction of the smooth muscle in the walls of the 'bronchial tree'.
- ▼ Carcinogens in tar may lead to lung cancer which can eventually destroy large parts of the lung, preventing gas exchange.

All the effects mentioned above are positively correlated with the number of cigarettes smoked, but there appears to be a significant genetic variation between individuals in the extent to which smoking affects lung function. Thus one individual may smoke only 5 cigarettes per day but develop severe emphysema by the age of 40 and lung cancer by 45, whilst another person may smoke 40 cigarettes per day and show no signs of associated ill health by the age of 90.

Even those exposed to the smoke of other people's cigarettes (**passive smoking**) are at an increased risk from a range of smoking related diseases. In families in which there is at least one heavy smoker, non-smoking individuals suffer 50% more respiratory illnesses than those coming from a non-smoking family. In addition, a large number of people have allergic reactions to tobacco smoke, which could be dangerous to those at risk from asthma, chronic bronchitis and CHD. A further subset at risk from passive smoking, are unborn babies who receive harmful substances from smoking across the placenta. Low birth weight, prematurity and increased risk of infant mortality are all associated with mothers smoking during pregnancy whilst perhaps as many as 1500 fetal deaths occur each year in the UK as a result of smoking.

CHRONIC BRONCHITIS and EMPHYSEMA

These two conditions are closely linked and often considered together even though they each have distinct symptoms and signs. Together they are referred to as chronic obstructive airways disease (COAD) or **chronic obstructive pulmonary disease** (COPD). Between them they affect 17% of British men and 8% of women in the 40-64 age group, and, worldwide, cause well over 2 million deaths per year. Both conditions are almost entirely due to cigarette smoking. Sufferers may become so disabled that they are breathless even at rest and require oxygen cylinders at home.

Chronic Bronchitis

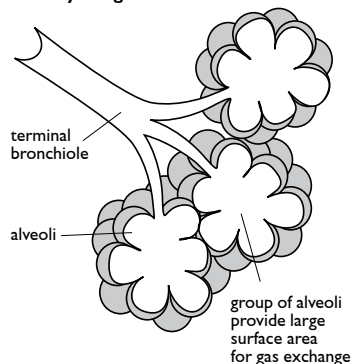
This is a clinical term and is defined as a chronic cough producing sputum (mucus from the lungs) for at least three months each year in two consecutive years. It involves inflammation of the bronchi and bronchioles which is caused by the irritant effect of tar and other substances in cigarette smoke. This inflammation causes thickening of the mucosal linings of these airways and over-secretion of mucus by glands in the larger airways and by goblet cells in the epithelium. These changes are responsible for the obstruction of the airways and in turn result in symptoms of wheeziness and breathlessness. In addition the excess mucus irritates the lungs causing the person to cough in an attempt to remove it. Further effects of bronchitis include increased frequency of lung infections, as bacteria thrive in the mucus. These infections, including pneumonia can make all the symptoms of bronchitis worse.

Emphysema

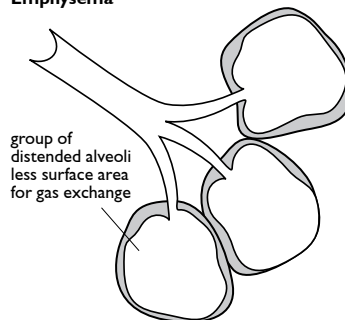
This is a condition defined by the enlargement of air spaces in the lungs as a result of the destruction of the walls of the alveoli. As these run together there is a reduction in the surface area over which gas exchange can occur. At the same time the airways become obstructed, and the lungs lose their elasticity. Instead of staying open during exhalation the smaller airways collapse preventing much of the air from being breathed out. Exhalation may require conscious effort. The result is breathlessness, fast, shallow breathing (hyperventilation), wheezing and difficulty in performing even basic activities such as walking short distances. The onset of emphysema is usually slow and gradual, and sufferers often live with this disabling disease for many years before death.

Like chronic bronchitis, emphysema is closely linked to smoking and the cause is thought to be related to the action of elastase and protease enzymes in the lungs. Such enzymes, released by granulocytes (white blood cells) break down the walls of the alveoli. Under normal conditions these enzymes work alongside anti-protease and anti-elastase enzymes, keeping a balance between breakdown and regeneration of alveoli. In smokers, however, an excess of breakdown activity occurs. There are two main reasons for this: firstly some anti-protease enzymes (such as 1-antitrypsin) are inactivated by chemicals in cigarette smoke. Secondly, there is an excess number of enzyme-secreting white blood cells in the alveoli of smokers owing to frequent infections. Another possible factor in alveolar damage is the frequent coughing associated with the chronic bronchitis which often coexists with emphysema.

Healthy Lung



Emphysema



Lung cancer

This is also known as **bronchial carcinoma** since it primarily affects the epithelial cells of the bronchioles. It is one of the most common causes of death in Britain and across the developed world. In excess of 35 000 people die from lung cancer each year in Britain, with a male: female ratio of 3.5:1. Over 90 % of these people are regular smokers. Non-smokers who contract lung cancer are often people who have been exposed to carcinogenic substances such as asbestos, coal products and oil based products through their work.

Like other types of cancer, lung cancer is caused by harmful mutations in genes controlling cell division, cell growth, and cellular adhesion. Such mutations affect the production or functioning of normal regulatory proteins and hence lead to rapid and uncontrolled cell division and growth. In the case of lung cancer the rate of mutations in epithelium cells is increased by carcinogenic (cancer-causing) chemicals in cigarette smoke, especially the tar which is thought to contain many such carcinogens.

Mutant cells will continue to divide unchecked by normal processes which regulate mitosis, to form a tumour (mass of cancer cells). These tumours may manifest themselves in different ways, but commonly they ulcerate, destroying the surrounding tissue and leading to the coughing up of blood which causes the patient to consult a doctor. Sometimes the tumour will cause chest pain as it presses on other structures within the chest cavity, such as the ribs, diaphragm and pleural membrane, or it may block a bronchus or bronchiole leading to collapse of part of the lung. In other cases, however, a tumour may grow undetected within the lungs without obvious symptoms. This means that in many cases lung cancer is diagnosed too late for treatment by surgery to be possible.

A few cells may break off the main tumour and be carried via blood or lymphatics to a distant site to form a secondary cancer (**metastasis**). Common sites for lung cancer metastases are in bones, the liver and the brain. It is often these metastases which eventually kill the patient.

◆ CHECKPOINT SUMMARY

- ◆ Tar irritates the delicate epithelia of the respiratory system stimulating the production of mucus.
- ◆ Tar and mucus increase the diffusion distance, and reduce the surface area, for gaseous exchange in the alveoli.
- ◆ Chronic bronchitis is diagnosed if a chronic cough producing mucus persists for at least 3 months each year in two consecutive years.
- ◆ Emphysema is marked by the destruction of alveolar walls and the running together of alveoli to form larger air spaces, resulting in the reduction of the surface area for gaseous exchange. Airways collapse and breathing becomes laboured.
- ◆ Chronic bronchitis and emphysema are so closely linked that they are also known collectively as 'chronic obstructive pulmonary disease'.
- ◆ Both conditions are almost entirely due to cigarette smoking.
- ◆ Lung cancer (bronchial carcinoma) can remain symptomless to an advanced stage of development, but in other cases is characterised by chest pains, blocked airways leading to breathlessness.
- ◆ The break away of cancerous cells to form tumours at secondary sites (metastasis) is common feature of lung cancer.
- ◆ The risks associated with smoking apply to 'passive' smoking, albeit at a lower rate.

EVALUATION of the EPIDEMIOLOGICAL and EXPERIMENTAL EVIDENCE LINKING CIGARETTE SMOKING to DISEASE and EARLY DEATH

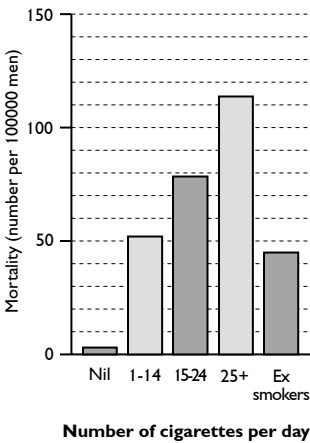
Epidemiological evidence is based on finding a statistically significant correlation between smoking and lung cancer using large numbers of people to generate enough data for statistical analysis (comparing, for example, observed and expected deaths across different groups). Any group of humans taken will differ in sex, age, exposure to environmental factors and genetic background, yet all of these differences need to be taken into account to ensure that just one factor is being investigated (this is the principle of the ‘fair test’, common to all scientific investigations.) However, it must be remembered, a statistically significant correlation does not prove a cause and effect relationship between the two factors. There can be a significant correlation between totally unrelated events.

Sir Richard Doll was responsible for demonstrating the strong links between smoking and lung cancer, chronic bronchitis and emphysema in a study which began in the 1950s. He used a technique known as the prospective study, where he identified his study group first and then recorded the deaths from smoking related diseases which occurred in members of the group over a number of years. His study population was male general practitioners (GPs) which was a particularly suitable choice: they were happy to be involved in a medical trial, were of broadly similar socio-economic groups, had similar lifestyles, occupations and exposures to other risk factors. Their main difference was in the numbers of cigarettes smoked per day: from 0 to over 30. In his study of 40 000 male GPs, Doll demonstrated that the risk of death from chronic bronchitis and emphysema in patients smoking more than 30 cigarettes per day was 20 times higher than that of non-smokers. The risk rose steadily with numbers of cigarettes smoked from 1-30 or more and was substantially decreased in ex-smokers. Further trials since then have backed up the original work.

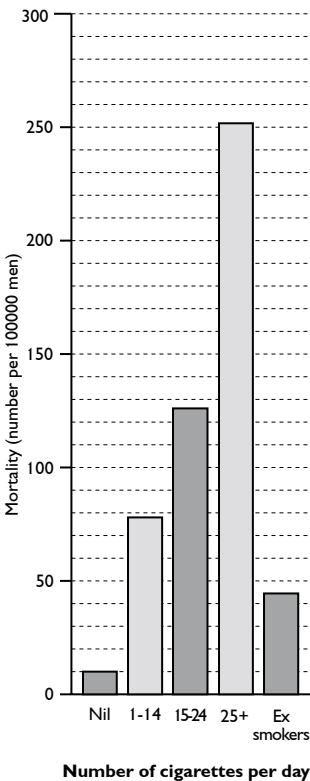
Similarly heavy smokers (more than 25 cigarettes per day) have a risk of lung cancer 25 times higher than non-smokers. Pipe smokers were at a lower risk, presumably because of lower amounts of inhalation.

Once a correlation is established, experimental evidence must be sought in order to establish a causal relationship e.g. smoking causes lung cancer. Such experiments invariably involve laboratory studies on experimental animals. Animal studies have shown that carcinogenic substances present in the tars can cause cancer when applied to the skin of mice. Further laboratory experiments have also shown that animals including mice and dogs can develop cancer of the larynx and lung from inhaling cigarette smoke. Whilst the links between smoking and lung cancer, bronchitis and emphysema are strikingly clear, they are still not appreciated by many people. Despite health education programmes, and the warnings which now appear on all cigarette packets and advertising material, smoking remains widespread. The British Government has set targets for a 30% reduction in smoking related diseases in men and a 15% reduction in women by 2010. It is essential that such programmes target young smokers since the earlier a person starts smoking, the greater is the risk of death from related illnesses.

Graph to show bronchitis death rates according to smoking habits



Graph to show death rates from lung cancer according to smoking habits



SMOKING and CARDIOVASCULAR DISEASE

As described earlier, smoking significantly increases the risk of a number of diseases of the cardiovascular system namely hypertension, atherosclerosis and CHD. This may result in death from a heart attack or myocardial infarction, or stroke resulting from blockage of cerebral vessels by blood clots or thromboses. In fact, as many as 40% of all deaths from cardio-vascular disease are thought to be due to smoking. A heavy smoker (over 25 cigarettes per day) under the age of 45 years may increase his or her risk of heart disease by over 15 times compared to a non-smoker. Whilst there are clear correlations between numbers of cigarettes smoked and risk of such diseases, the exact causal mechanisms are not clear. The following effects have however been suggested.

The effects of nicotine and carbon monoxide

Nicotine is the addictive component of cigarette smoke and has a number of effects on the cardiovascular system. It stimulates the release of adrenaline and noradrenaline; two hormones which increase blood pressure (hypertension) by causing the blood vessels to constrict, and heart rate and cardiac output to increase.

Carbon monoxide (CO) a colourless, odourless, poisonous gas found in tobacco smoke combines irreversibly with haemoglobin in red blood cells producing carboxyhaemoglobin. This compound cannot carry oxygen so the oxygen carrying capacity of the blood may be reduced by over 15% in heavy smokers. (The levels of the gas in the lungs of a smoker can be over eight times the level of carbon monoxide permitted in industry.)

Atherosclerosis

Nicotine increases the concentration of fatty acids in the blood which may contribute to increasing deposition of atheroma leading to atherosclerosis. Carbon monoxide, along with nicotine, is also toxic to the endothelial lining of arteries and is thought to be one factor which may cause damage to this lining and allow cholesterol to enter the vessel wall causing development of atheromas.

Coronary heart disease

The increased blood pressure (hypertension), heart rate and cardiac output, caused by nicotine, place extra strain on the heart and can be serious for the person who has already had a coronary attack or who is exposed to other risk factors for CHD, such as obesity or diabetes. Nicotine also makes the heart more irritable and can precipitate dangerous irregularities in heart beat. A lower rate of oxygen delivery to tissues as a result of the irreversible combination of carbon monoxide with haemoglobin may cause the heart rate and blood pressure to increase, which may be risk factors in cardiovascular disease. Also deficiencies of oxygen may cause angina and contribute towards a heart attack where insufficient oxygen is supplied to the heart muscle.

◆ CHECKPOINT SUMMARY

- ◆ Epidemiological studies can be cross-sectional across all members of a particular group, or prospective (longitudinal), following a group of subjects over a long period of time.
- ◆ Sir Richard Doll's prospective study on male Doctors started in the 1950s first raised the correlation between smoking and bronchitis, emphysema and lung cancer:
- ◆ Correlation does not prove cause and effect. Two totally unrelated effects can be perfectly correlated.
- ◆ Despite the accumulating evidence, many still resist the conclusions.

Stroke

Nicotine also increases the likelihood of blood clotting within blood vessels which can lead to the development of blood clots or thromboses. This effect is mediated in several ways: nicotine and other components of tobacco smoke are thought to increase the 'stickiness' of blood platelets, the small cell fragments involved in normal blood clotting, causing them to adhere to the surfaces of damaged atheromatous areas. At the same time more fibrinogen (one of the proteins involved in blood clotting) is produced while lower levels of enzymes which break down blood clots are found. Blood clots formed in the coronary arteries may block the artery leading to a myocardial infarction or heart attack. Alternatively the clot may be dislodged and travel in the blood (as an embolus) to the brain where it may block a cerebral vessel, depriving part of the brain of oxygen and causing a stroke.

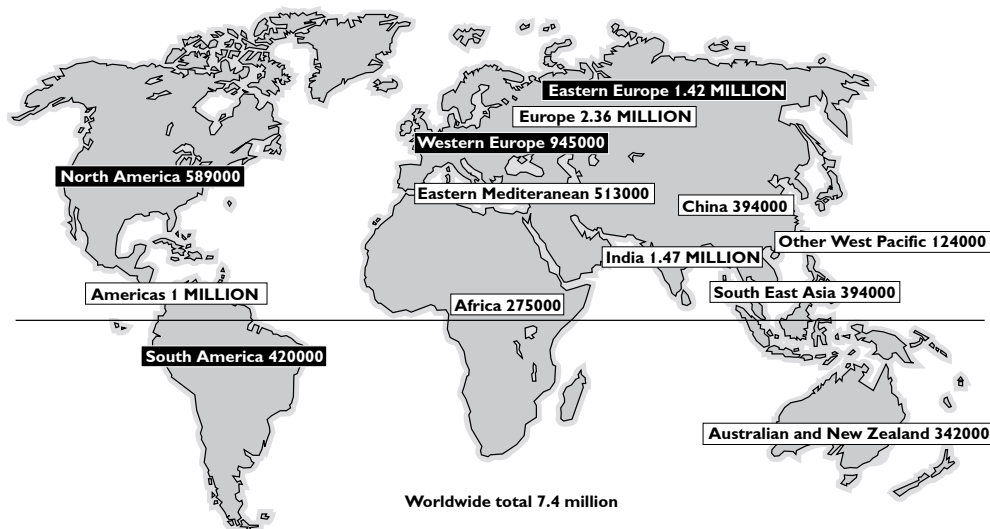
GLOBAL DISTRIBUTION of CORONARY HEART DISEASE (CHD)

In 1999 it is estimated that all cardiovascular diseases, including Coronary Heart Disease (CHD), killed 16.7 million people worldwide. In common with other non-infectious diseases, CHD is more common in developed countries compared to developing countries. This statement, however, masks the fact that CHD is becoming very common in many developing countries, particularly in urban regions. Up to 25% of deaths in those aged 50-65 in developing countries are from CHD, with 1.47 million people dying of CHD in India alone in 1999, a figure which is expected to double within the next 20 years. On the other hand, many developed countries such as France, and Japan have very low death rates from CHD. It should also be noted that whilst CHD is currently one of the main causes of death in developed countries, in many of these, including England and the United States, the rate has been declining since the 1970s.

CHD is closely associated with the changes in lifestyle which accompany urbanisation and increased affluence. These include increased food intake particularly of saturated fat, sugar, alcohol and salt in the diet, decreased physical activity due to more sedentary occupations and the high level of car ownership. Increased cigarette smoking and increased mental stress are other important factors. It is also associated with old age, so wherever life expectancy increases so too does the rate of CHD.

In addition to the recognised risk factors there seem to be other subtle genetic and environmental differences between ethnic groups which are also significant. This may explain why the risk of CHD is greater in those of Indian origin living in the UK compared to that of Caucasians (whites), even when lifestyle differences are taken into account.

Global distribution of deaths from Coronary Heart Disease (CHD) 1999



CORONARY HEART DISEASE: The **BALANCE** between **PREVENTION** and **CURE**

Prevention

Prevention is always better than cure. As the risk factors for the development of CHD are becoming clearer, there are many recommended ways by which individuals can reduce their own risk of developing the disease. Such preventative measures should be put into action early in life since there is evidence that atheroma build-up may begin in childhood when bad dietary habits, insufficient exercise, and smoking often begin. Schools and other community institutions need to increase the emphasis on healthy lifestyle, as do general practitioners and other health professionals. Basic measures to prevent or rather reduce the risk of CHD include:

- ▼ Never starting to smoke or stopping if a smoker.
- ▼ Reducing the amount of saturated fat in the diet and the overall number of calories eaten. Ideally less than 30% of calories taken should come from fats.
- ▼ Losing weight so that body mass index (BMI Section 5.2.2) is below 25.
- ▼ Reducing salt intake which reduces the volume of the body fluids.
- ▼ Increasing the amount of exercise taken to a minimum of three twenty minute sessions per week. These can include gentle exercise such as walking but in young people should involve more vigorous exercise.

The above list of preventive measures may be taken by all individuals whatever their age or current risk of CHD. Such measures will also help to lower the risk of CHD in individuals who have put themselves at high risk through smoking and other activities. It should be noted that changes of lifestyle aimed at preventing CHD can have a range of other health benefits to the individual and to society as a whole. Thus reducing smoking will also reduce the risk of respiratory diseases and many cancers, while increasing exercise levels and losing weight may increase the mental well being and confidence of an individual.

Under medical supervision additional measures might be appropriate for high risk groups. Medical evidence is emerging that those at risk of CHD might benefit from taking small amounts of aspirin each day to reduce the risk of blood clotting and hence the development of thromboses.

Cure

Cure or treatment of those patients who have already developed CHD involves a range of treatments.

Drug therapy of which there are three main classes: nitrates which dilate coronary arteries, calcium antagonists which dilate coronary and peripheral arteries and reduce oxygen consumption by the heart, and beta-blockers which reduce cardiac output by lowering the heart rate and the force of contraction of the heart muscle.

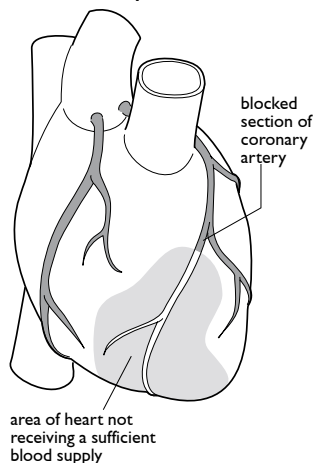
Coronary by-pass surgery is suitable for a small proportion of patients with CHD. This involves by-passing the narrowings of the coronary arteries using pieces of artery or vein taken from elsewhere in the patient's body, restoring a blood supply to the deficient region. The piece of vessel is grafted onto a healthy artery (often the aorta) at one end and onto the damaged artery downstream of the blockage at the other, diverting the blood around the blockage and restoring blood supply to the heart muscle. Sometimes more than one artery may be by-passed at a time, hence the terms double and triple by-pass. One advantage of using a piece of blood vessel from a patient's own body in this operation is that it avoids rejection of the tissue.

Currently over 20 000 by-pass operations are performed in Britain each year, but this figure is lower than in some other countries and the Government is aiming to increase the number in a new bid to cut deaths from heart disease and stroke.

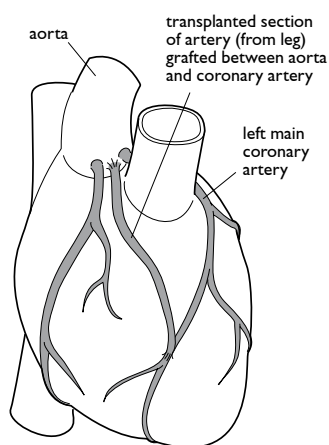
Heart transplant surgery was first performed in 1969. It involves the removal of the diseased heart of an individual (the recipient) and its replacement with a healthy heart from a donor who is brain stem dead. The donor heart is connected to the blood vessels of the recipient, although the recipient's right atrium, containing the sino-atrial node (pacemaker) is usually retained to initiate the heart beat (see 5.3.2).

Heart transplants are major surgical procedures which carry a risk of death associated with the surgery itself of between 10-20%, and are only performed as a last resort. They may, however, offer the only hope of recovery from many types of heart disease, including some congenital defects in children, as well as for a very small number of patients suffering from CHD. 60% of patients now survive for at least five years after a heart transplant, many leading active lives.

Heart before operation



Heart after operation



In all cases it is necessary to find a heart with a suitable 'tissue type' (having cells with similar surface antigens to those of the recipient) to prevent rejection of the organ by the immune system of the patient. This occurs because the cells of the transplanted heart are recognised as foreign by T-lymphocytes within the blood stream and attacked by them. Immuno-suppressant drugs are given to reduce this problem, but inevitably they increase the risk of infection.

Whilst heart surgery (particularly by-pass grafts) may cure some individuals of life threatening heart disease and allow them many years of good health, in other cases the benefits of these expensive procedures can be short lived. Individuals who have previously had a high-risk lifestyle in terms of CHD, for example through smoking, high fat diets and lack of exercise, may in some cases, return to their former habits after surgery. Thus by-pass grafts themselves may become narrowed through atheroma build up leading to further angina and myocardial infarction, especially in smokers. There are many ethical and financial issues involved here, particularly when health services are under financial pressure and only limited numbers of operations can be performed.

It could be argued that patients due for heart surgery must make life-style changes before their surgery and maintain these afterwards. A particular focus should be on giving up smoking, losing weight and taking more exercise. A more extreme view is that priority surgery be given to those individuals who have taken preventative measures, but who have still developed CHD (perhaps those who have juvenile diabetes which has led them to develop hypertension, or those who have a genetic predisposition to high levels of blood cholesterol). Others argue that organ donors or their families should be able to choose the type of person (e.g. a non-smoker) to whom an organ should be given, or suggest that patients should contribute towards the cost of hospital treatment for 'self-inflicted' diseases. Due to shortage of hearts and other organs there is also the controversial issue as to whether organ donation should operate on an 'opt out' policy rather than the current 'opt in' system.

Whilst some of these positions are extreme and are not yet practised in the health service they do raise the question of an individual's responsibility for his or her own health. This is particularly true where preventative measures are well known and can be followed relatively easily.

◆ CHECKPOINT SUMMARY

- ◆ Nicotine is the addictive drug in tobacco smoke.
- ◆ Nicotine stimulates the release of adrenaline and noradrenaline, which in turn result in high blood pressure, increased heart rate and cardiac output.
- ◆ Nicotine increases the levels of fatty acids in the plasma of the blood, damages the lining of blood vessels, leading to atheroma and atherosclerosis.
- ◆ Nicotine increases the tendency for the blood to clot, and hence the formation of internal clots (thromboses).
- ◆ Tobacco smoking is the major cause of leg amputation in the UK, as a result of atherosclerosis and thrombosis in the legs.
- ◆ Nicotine causes dangerous irregularities in the electrical activity of the heart.
- ◆ Carbon monoxide combines irreversibly with haemoglobin preventing its ability to deliver oxygen to the tissues.
- ◆ The combined effects of tobacco smoking greatly increases the risks of all cardiovascular disease.
- ◆ Coronary heart disease (CHD) is more common in developed countries, although exceptions exist such as France and Japan.
- ◆ CHD is closely associated with the changes in lifestyle which accompany urbanisation and increased affluence.
- ◆ Prevention is always better than cure, measures include non-smoking, reducing dietary saturated fats, keeping the BMI below 25, reducing salt intake, and increasing the amount of aerobic exercise.
- ◆ Cure involves drug therapy, coronary by-pass surgery and heart transplants.

Infectious Diseases

Content

- ▼ Cholera, malaria, tuberculosis (TB) and AIDS
- ▼ Antibiotics

Learning Outcomes

Candidates should be able to:

- a) describe the causes and means of transmission of cholera, malaria, AIDS/HIV and TB. (Knowledge of the symptoms of these diseases is not required)
 - b) assess the worldwide importance of these diseases.
 - c) describe the roles of social, economic and biological factors in the prevention and control of these diseases.
 - d) outline the role of antibiotics in the treatment of infectious disease.
-

CAUSES and MEANS OF TRANSMISSION of CHOLERA, MALARIA, AIDS/HIV and TB, their WORLDWIDE IMPORTANCE, and the ROLES of SOCIAL, ECONOMIC and BIOLOGICAL FACTORS in the PREVENTION and CONTROL of these DISEASES

Introduction

Infectious diseases are diseases caused by pathogens (mainly bacteria, viruses, fungi and protoctists) which can be transmitted from one person to another in a variety of ways. The four diseases mentioned above, cholera, malaria, tuberculosis and HIV/AIDS, have all proved very difficult to prevent and control and there is very little chance of any of them being eradicated in the foreseeable future. There are many reasons for this, which include biological features of the pathogens themselves, as well as social and economic conditions of the human populations who suffer from them.

Reducing the number of deaths from each of these diseases involves a range of strategies which include modern medical treatments as well as simple improvements in living conditions, sanitation and education. In all cases there are two primary aims which are often closely linked. Firstly it is important to prevent people from becoming infected in the beginning (**disease prevention**). Secondly those who do catch the diseases must be managed and treated to ensure that the diseases do not spread through the population and cause epidemics. This is known as **disease control**.

Worldwide importance of infectious diseases

World-wide, infectious diseases cause 25% of all deaths, and are the most important causes of death in children and young adults (13 million deaths per year). In many countries especially in Africa they represent over 80% of all deaths. WHO estimates for 1999 show, for example, over 3.5 million deaths world-wide from respiratory infections (excluding tuberculosis), 1.5 million deaths from tuberculosis (TB), over 2 million from diarrhoeal diseases including cholera, 1.2 million from malaria and 2.6 million from HIV/AIDS. In addition to the deaths, such diseases also cause serious illness in thousands of millions of other people.

The majority of these deaths now occur in the developing world, yet less than a century ago infectious diseases, especially TB, were also the most common causes of death in Britain and other European countries. In the past fifteen years, however, the appearance of HIV, the dramatic resurgence (increase after a previous decline) in cases of TB and the appearance of antibiotic resistant bacteria (including some strains of those causing TB), has demonstrated that infectious diseases are still a threat to health in the developed world. Air travel and increasing population movements also bring risk of infectious diseases to more people in the developed world.

Table of mortality statistics from 1999: Africa, containing many of the poorest 'developing' countries compared to Europe, containing some of the wealthiest 'developed' countries

	Africa	Western Europe
Total Pop	600 000 000	392 000 000
Cause of death		
All non-infectious diseases	2 100 000 (21.9)	3 499 000 (88)
All infectious diseases	4 600 000 (47.9)	51 000 (1.3)
HIV/AIDS	1 800 000 (18.7)	12 000 (0.3)
Respiratory infections	806 000 (8.3)	155 000 (3.9)
Diarrhoeal diseases	731 000 (7.6)	4000 (0.1)
Tuberculosis	209 000 (2.2)	7000 (0.2)
Malaria	961 000 (10.0)	none
Total deaths	9 600 000	3 974 000

All figures in thousands
Percentage of Total deaths in brackets

Cholera

Cause - Cholera, a disease characterised by severe diarrhoea and death from dehydration, is caused by the bacterium *Vibrio cholerae*. Whilst it was once common in Britain and across the world it is now mainly found in the poor developing countries and particularly in overcrowded regions within these countries. It is a major cause of death and illness in these regions, often occurring in epidemics. It is estimated that around 6 million cholera infections occur per year, worldwide, with at least 120 000 deaths.

Transmission is usually via drinking water or food which is contaminated with infected faeces containing the cholera bacteria.

This means of transmission is sometimes known as the **faeco-oral route**. Flies which land on infected faeces and then on foodstuffs can also spread the disease. In addition, cholera may be spread by eating shellfish which have lived in contaminated water.

Owing to its mode of transmission, cholera may spread extremely rapidly from one infected person to hundreds of others. This spread does, however, rely on poor sanitation, including a lack of toilet facilities and an absence of clean drinking water. Unfortunately such conditions still exist in many developing countries, where sewage enters the same rivers or streams which are used to bathe in and drink from. These conditions are made worse in the slums of large cities such as Calcutta in India, and Sao Paulo in Brazil, in makeshift camps following disruption by famine, war or natural disasters, and when large groups of people come together for religious festivals or other celebrations. Recent epidemic outbreaks have occurred, for example, in the Peruvian shanty town of Belén in 1991 (during a larger cholera epidemic in Peru) and in the refugee camps during the Rwandan crisis of 1994.

Prevention and control is mainly by improving sanitation and reduce overcrowding. Chlorination of water, the provision of piped water, of latrines (toilets) and sewage treatment facilities can lead to drastic reductions in the number of cases of cholera. Measures to reduce flies which can transmit the disease from faeces to food are also important.

Education is also crucial to ensure that people understand and practise basic hygiene. In particular it is vital that the link between faeces and disease is clear. People should be encouraged, for example, to wash their hands after using the toilet, to boil water before drinking it and to avoid defaecation in or near streams and rivers.

Yet although these measures may sound simple, the provision of adequate sanitation systems is very expensive. Countries must often rely on overseas money (aid) to pay for these and for the education programmes which can be difficult to implement.

In addition to these measures a cholera vaccine is available. Whilst this is useful for people travelling to areas where cholera is endemic and for use in such regions during epidemics it is not very effective and it only last a few months. It is hoped that a new, genetically engineered vaccine using a live attenuated (weakened) bacterium with two of its toxin genes deleted will prove more effective.

Once people are infected with cholera the disease can be controlled in a number of ways if medical facilities are available. Patients and their close contacts (family members or work colleagues) may be treated with antibiotics or given vaccinations. Patients should also be closely monitored and have their faeces disposed of in a hygienic fashion. Oral rehydration therapy, the provision of water mixed with appropriate quantities of salts and sugars, to replace lost fluids, is very effective in treating the disease.

Malaria

Cause - Malaria is caused by a single celled parasite, *Plasmodium*, which invades the liver cells and red blood cells of humans. There are four species which affect humans, but the most common are *Plasmodium vivax* which usually causes a relatively mild infection, and the virulent *Plasmodium falciparum* which is responsible for most malaria deaths. Although some areas which previously experienced malaria are now free of the disease (such as the United States and parts of Europe) one third of the world's population still lives in malarious regions. The disease is particularly severe in sub-Saharan Africa, where in parts, up to a quarter of children die of the disease, and almost everyone becomes infected several times during their lives. Over 1 million people died of the disease worldwide in 1999.

Transmission from one person to another is by the bite of an infected female *Anopheles* mosquito (the vector). As shown in the diagram below, the mosquito is not simply a passive carrier of the disease: the malarial parasite must complete part of its life cycle in humans and part inside the female mosquito.

A malaria infection of a human starts when a female mosquito injects malaria parasites known as **sporozoites** in its anti-coagulant saliva into a human on which it is feeding. These parasites migrate to the liver cells where they reproduce **asexually**, and develop into merozoites which then infect red blood cells. Here they also reproduce asexually, producing huge numbers of additional merozoites which burst out of the red blood cells and cause the characteristic fever and other symptoms of the disease. Some merozoites develop into gametocytes which can be taken up when another female mosquito feeds on the infected person's blood. Once inside the body of the mosquito these gametocytes fuse, the resulting zygotes develop into sporozoites and move into the salivary glands of the female mosquito where they can be injected into another person. The cycle thus begins again.

Worldwide distribution of malaria

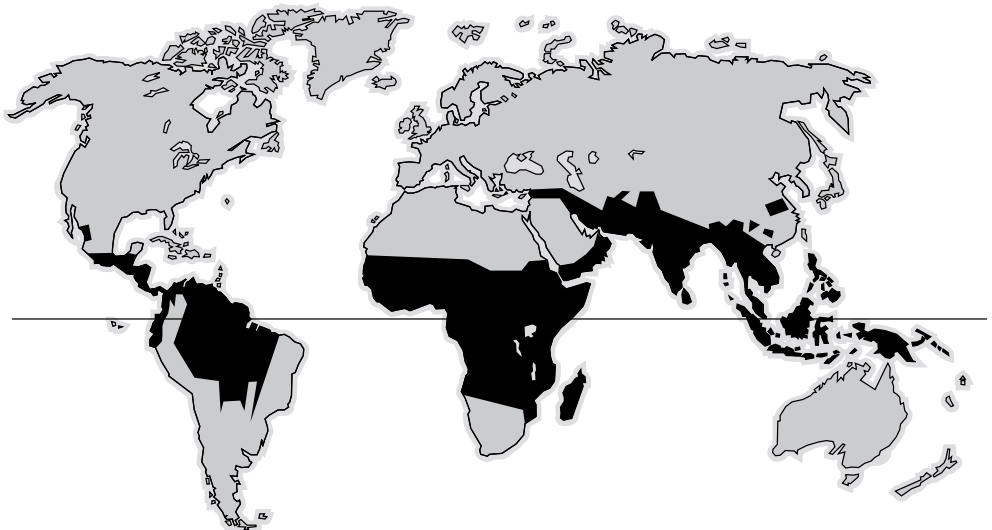
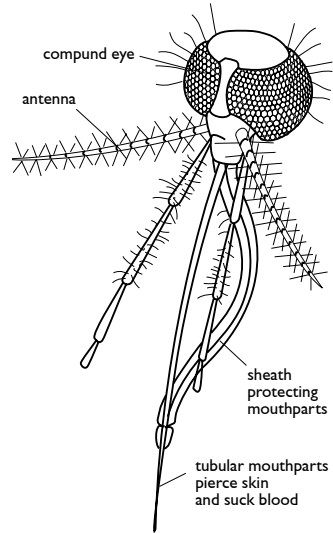
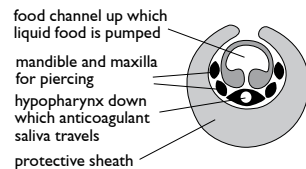


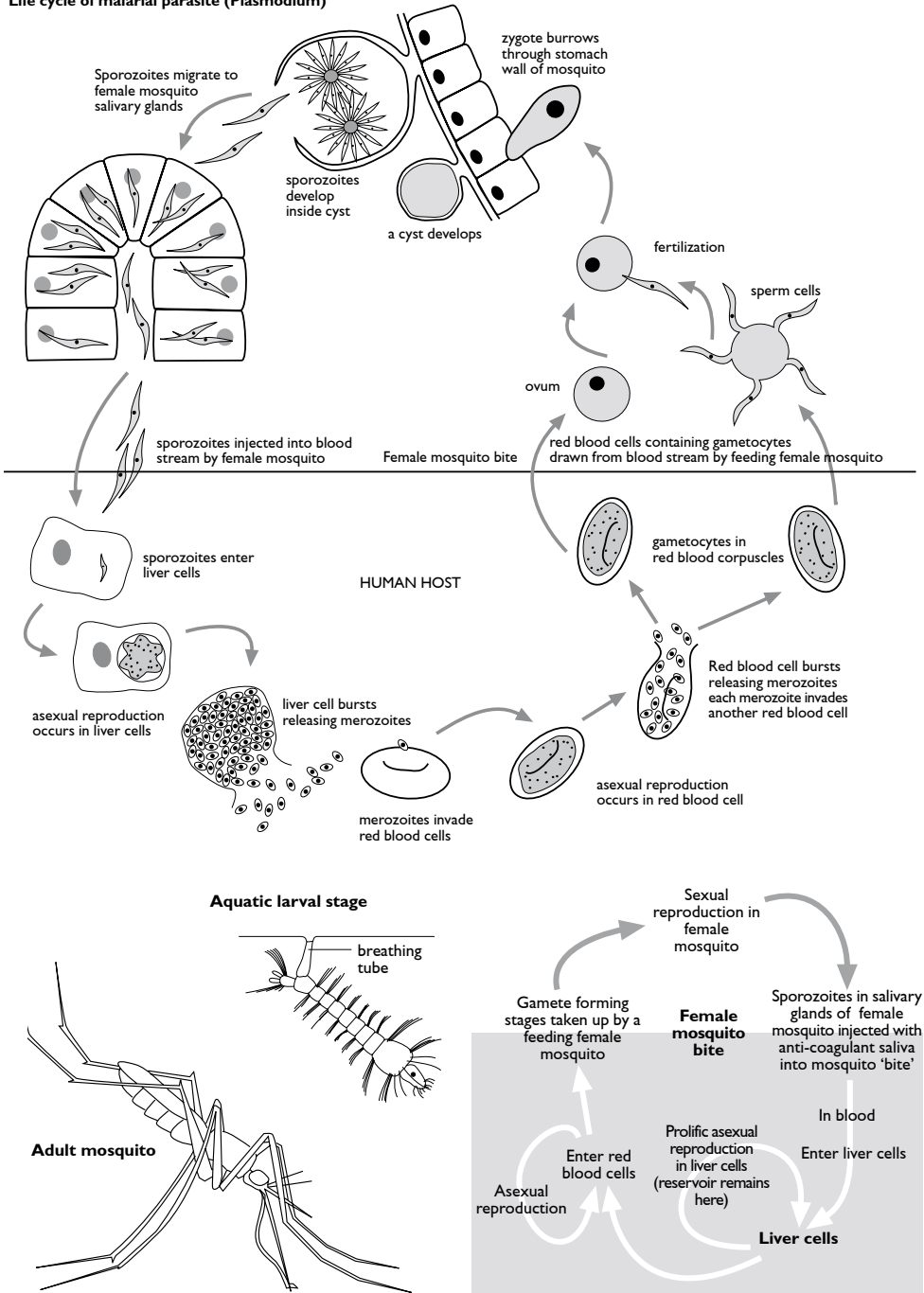
Diagram to show mosquito mouthparts



Section through mouthparts



Life cycle of malarial parasite (Plasmodium)



Prevention and control is mainly by reducing the risk of mosquito bites and measures include:

- ▼ Drainage of marshy areas and removal, where possible, of any exposed areas of water, including puddles, disused cattle troughs, old tyres etc., to prevent mosquitoes breeding (the female mosquito lays her eggs in water and the larvae and pupae are aquatic but air breathing).
- ▼ Placing oil on the surface of water which prevents mosquito larvae and pupae from obtaining oxygen and hence causes their death.
- ▼ Killing the mosquito vector with insecticides and/or killing the larvae with larvicides.
- ▼ Using biological control in the form of fish which eat mosquito larvae in the water
- ▼ Encouraging people to protect themselves from being bitten by female mosquitoes by sleeping under bed nets, wearing protective clothing and using insecticide sprays and repellants.

In addition, anti-malarial drugs and the plants from which they are derived, which inhibit the growth of the malaria parasite inside humans have been used for hundreds of years. These include quinine and synthetic drugs such as chloroquine and mefloquine. There is, as yet, no effective malaria vaccine.

Anti-malarial drugs may be used as prophylaxis (to prevent disease occurring by taking the drug in advance of exposure to malaria) as is done in some community prevention programmes, or as treatment following infection. Such drugs can thus form an important means of controlling the disease in individuals who are infected, improving their condition and reducing the likelihood of the disease being passed onto others. It is also important to ensure that infected individuals have access to medical facilities (including transport to treatment centres) and sufficient education to recognise the symptoms of malaria and to seek help early.

Whilst there are many measures available for the prevention and control of malaria, these are not always successful. By the 1950s drainage measures and the use of the insecticide DDT had eliminated malaria from parts of the United States and Europe but these had less impact in tropical regions of the developing world. There are many reasons for failure which include:

- ▼ Mosquitoes breed in the tiniest bodies of water, so even if swamps are drained the insects will exploit puddles, flower pots or even hoof-prints with a few millimetres of water.
- ▼ Expense and logistical difficulties have hindered mosquito control programmes. To be effective they must reach all areas of a country, yet often poor roads, mountainous terrain and civil unrest prevent access to some regions. Since mosquitoes can fly and travel distances of several kilometres any control campaign must be carried out on both sides of national boundaries.
- ▼ Mosquitoes developed resistance to DDT as a result of a gene mutation. This spread rapidly through mosquito populations due to their short generation time and large reproductive potential, rendering the insecticide ineffective by the late 1960s.
- ▼ Similarly malaria parasites developed resistance to anti-malarial drugs, especially chloroquine. Chloroquine resistance was first noted in the 1970s in South East Asia but has now spread throughout Asia and Africa. Resistance has developed to many other anti-malarial drugs and there are regions where no anti-malarial drugs are effective.

◆ CHECKPOINT SUMMARY

- ◆ Malaria is caused by the single celled parasite (*Plasmodium*) and transmitted via a female mosquito vector (*Anopheles*).
- ◆ Malaria causes over 1 million deaths per year, primarily in sub-Saharan Africa, and other parts of the developing world. It was once common in the United States and parts of Europe.
- ◆ The malaria parasite lifecycle is complex and involves a sexual stage in the female mosquito and asexual stages in the liver and red blood cells of humans.
- ◆ A human can only become infected with malaria when an infected female mosquito feeds on their blood. In turn a female mosquito can only become infected if it takes a blood meal from an infected person
- ◆ Malaria prevention and control is focused on preventing people being bitten by mosquitoes. This includes individual protective measures as well as regional, national or international efforts to control mosquitoes.
- ◆ Malaria prevention and control also uses various anti-malarial drugs. There is no vaccine.
- ◆ There are biological, economic and political reasons why malaria control is difficult.
- ◆ Biological reasons include the fact that malaria parasites acquired resistance to anti-malarial drugs, that mosquitoes acquired resistance to DDT, and that mosquitoes need only tiny amounts of water to breed.
- ◆ Malaria control is very expensive and needs years of sustained international effort and cooperation. This has often proved difficult.

Tuberculosis

Cause - Tuberculosis or TB is primarily a disease of the lungs and respiratory tract and is caused by a bacterium called *Mycobacterium tuberculosis*. The bacterium multiplies in and destroys the lung tissue. It also suppresses the immune system making it harder for the body of an infected person to make an immune response against the disease. It can also infect other parts of the body, including the bones, gut and kidneys.

The World Health Organisation estimates that over 1.5 million people died of TB worldwide in 1999, with several times that number being infected with the disease. The majority of these sufferers are in the developing world, but the disease is also becoming increasingly common again in Europe and the United States where it was once a leading cause of death. There were, for example, 7000 deaths in Western Europe in 1999, an enormous increase over figures from as recently as 10 years ago.

Transmission of TB is by airborne or droplet infection, which means that it is transmitted from one person to another via microscopic infectious water droplets in the air. When a person infected with TB coughs, he or she releases thousands of such droplets containing bacteria which may be breathed in by other people who are close by. Usually, however, a person needs prolonged contact with an infected person to develop the disease: it is not as infectious as the common cold or influenza.

TB is most easily spread, and hence most common, where people live or work in crowded conditions where there is little fresh air. Unfortunately such conditions are frequently found in the poorer regions of cities of the developing world, in refugee camps, in prisons, and in dormitories or centres for the homeless which are becoming increasingly common in the developed world.

TB is much more likely to cause disease in people whose immune systems have been weakened by infections with other diseases (especially HIV - see below) or through malnutrition. Such conditions are more common in the circumstances of poverty, war or social disadvantage.

Another form of TB, *Mycobacterium bovis*, can be spread through unpasteurised milk and milk products.

Prevention and control of TB is best achieved by preventing the bacterium from spreading, by improving living and working conditions of the population. Measures include:

- ▼ Reducing overcrowding in homes and workplaces.
- ▼ Improving ventilation in buildings so that fresh air can circulate. This also includes reducing the amount of smoke or dust in the atmosphere as inhalation of such particles can inflame the lungs and make them more susceptible to infection with TB.
- ▼ Improving the overall health and nutrition of the population to ensure that the immune system is fully functional.

It was a combination of these measures which lead to dramatic reductions in deaths from the disease in Britain even before the tuberculosis bacterium was discovered in 1882. Later, when the cause of the disease and its mode of transmission were understood, infected people were isolated to prevent spread.

A TB vaccine, known as BCG (Bacille Calmette Guerin after the scientists who developed it, using an attenuated (weakened) strain of bacterium, in the 1920s) has been used extensively since 1954. Although this vaccine is widely used in the developing and developed world, it does not offer 100% protection against TB. It is only effective in those who have not been exposed to the bacterium before and its effectiveness seems to vary considerably between populations.

Control of TB in infected people is heavily reliant on antibiotics, which have been available since the 1940s. In addition to treating infected people, control programmes often aim to find and test contacts of these people for TB infection and, if necessary, treat them as well. Yet, in spite of decades of effective treatment by antibiotics, many strains of TB bacteria are now resistant to such drugs. Some strains are known as multi drug resistant-TB (MDR-TB) and are effectively untreatable. One reason for this is thought to be the fact that the cure of TB requires very long courses (up to 12 months) of a combination of antibiotics. Often patients prescribed such long courses will fail to complete them because the drugs have unpleasant side effects or because people move away from the area and fail to attend clinics. This increases the chance of bacterial resistance developing to some or all of these antibiotics (see section on antibiotics). Once such dangerous strains emerge they can then be passed on to other people and spread through the population. Other factors are increasing population density, especially in cities, increasing poverty, declining living conditions, including increased homelessness, and the rise of HIV/AIDS.

- ▼ Tuberculosis (TB) is caused by a bacterium (*Mycobacterium tuberculosis*) which infects the lung and other tissues.
- ▼ TB currently kills over 1.5 million people per year. Most of these deaths are in the developing countries but its frequency is increasing across the world.
- ▼ The disease is spread via droplets in the air, and hence is spread most rapidly in overcrowded, underventilated areas.

◆ CHECKPOINT SUMMARY

- ◆ Prevention of TB is focused on improving living and working conditions and improving the overall nutrition and health of individuals. A vaccine is also available but is not effective in all cases.
- ◆ Control of TB in infected patients relies on long courses of antibiotics. Often a combination of antibiotics is taken.
- ◆ Two of the reasons for increases in TB cases and deaths in the past decade have been the emergence of antibiotic resistant strains of TB and the rise of HIV/AIDS which increases susceptibility.

HIV/AIDS

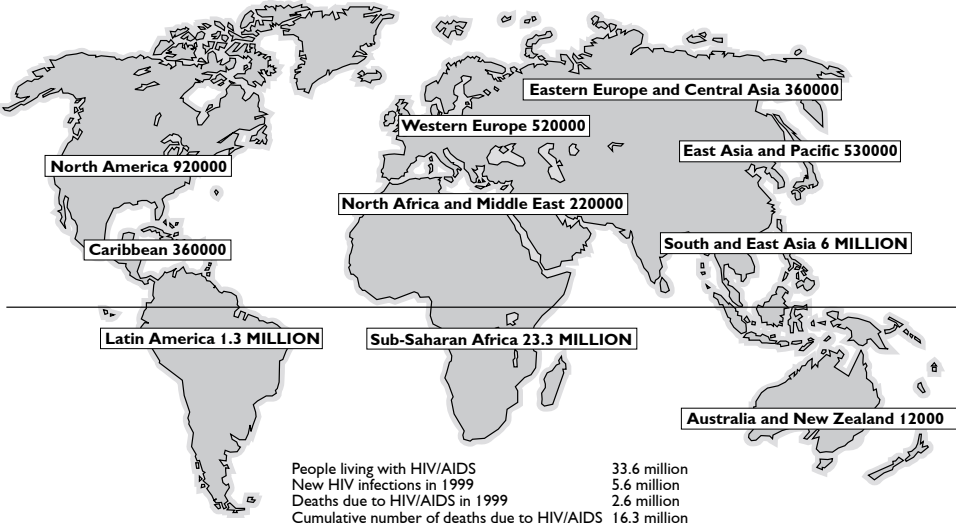
Cause - Acquired Immune Deficiency Syndrome (AIDS) results from infection with the Human Immunodeficiency Virus (HIV). There are two types of this virus known as HIV-I and HIV-II. The former is more virulent and responsible for most AIDS deaths. As its name suggests, AIDS is a disorder where the body's immune system is damaged preventing it from fighting common infections. This happens because the HIV virus lives and replicates inside **Helper T-lymphocytes** and prevents them from 'helping' B and T lymphocytes to work (section 5.2.6). Not all people infected with the HIV virus (HIV antibody positive people) go on to develop AIDS although the vast majority do. The period of time between infection and development of AIDS is highly variable (from 2 to 15 years), but once AIDS is diagnosed, death from infectious diseases, especially pneumonia and TB, or from a range of cancers will eventually occur.

AIDS was not recognised as a disease until the early 1980s, but has spread rapidly since that time. It is now regarded as a **pandemic**. It is estimated that at least 33 million people are infected with HIV today. The continent most affected at present is Africa, where 70%

of HIV cases are found, but the number of cases in Asia, is increasing rapidly. Over 2.6 million deaths per year now result from the disease, which are concentrated in young heterosexual people in the developing world. However, the importance of the disease in the developed world should not be overlooked. HIV/AIDS has taken the developed world by surprise, proving that new and deadly infectious diseases can still emerge.

The significance of the AIDS pandemic extends far beyond the simple tally of deaths resulting from the disease. Firstly, many of its victims are young adults. Some experts have suggested that this could result in a reduced workforce in some areas leading to a slowing of economic progress. Future population growth may also be affected. Secondly, the rise of HIV/AIDS and its effects on the immune system have led to a resurgence of TB and other infectious diseases. Once such diseases gain a foothold in AIDS patients they can then be transmitted to other people in the community. Thirdly, HIV/AIDS kills people slowly, meaning that they often require hospital treatment for many years. With so many new cases, and not enough money for medical services, it is possible that spending on other diseases such as malaria will be reduced, causing more deaths from these and other causes.

Worldwide distribution of adults and children estimated to be living with HIV/AIDS 1999,



Transmission occurs in several ways all of which involve a direct exchange of body fluids between an HIV infected person and an uninfected recipient. There are no recorded instances of transmission via saliva or sweat. The main modes of transmission are:

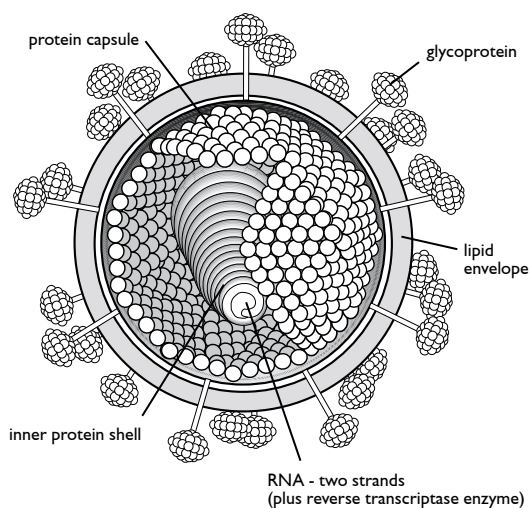
Sexual contact. 90% of people with HIV have caught it through vaginal or anal intercourse or oral sex with infected people. This relies on infected semen or vaginal fluid entering the blood stream of a recipient, often through cuts or sores. Heterosexual activity is most significant in terms of overall numbers of HIV infections transmitted but anal intercourse carries a higher risk of infection as the rectum is easily torn.

Blood contact. HIV infected blood may enter the bloodstream via needles used for intravenous(injected) drugs, from transfusions of blood or blood products, or during a range of medical procedures such as vaccinations.

Mother to child. HIV may pass from mother to fetus via the placenta, from mother to baby at birth when blood contact may occur or during breast feeding. HIV-II is more commonly transmitted in this way.

Prevention and Control involves a range of procedures to prevent transmission of infected body fluids. Since most HIV cases arise from sexual contact, one of the most important ways of preventing

Human Immunodeficiency Virus



further spread is through programmes emphasising 'safe sex'. Educating people about HIV/AIDS, and encouraging them to avoid casual sexual contact, reduce the number of sexual partners and use **condoms** all markedly reduce the risk of catching HIV. Such programmes are in place across the world, but following their advice does require changes in social behaviour. Many people are reluctant to talk about sexual behaviour (or sexually transmitted diseases) and are also reluctant to use condoms, even if they are provided free. In some areas, however, condoms are not available, or are expensive to buy, whilst in other regions religious beliefs may inhibit the use of contraceptives.

The fact that carriers of the disease may transmit it for years before they know they are infected further hinders preventative measures. Even when an HIV test is taken it is not 100% accurate, especially during the early stages of infection where it may give a false negative result. Also many people who suspect that they are infected will not seek such a test as they know there is no cure if they are HIV positive. In developed countries, those known to be HIV positive will be monitored for signs of AIDS and treated if these symptoms

◆ CHECKPOINT SUMMARY

- ◆ Cholera is caused by a bacterium and mainly spread through infected water and food.
- ◆ Cholera was once common in Europe but is now mainly restricted to the developing world where it causes over 100 000 deaths per year.
- ◆ Cholera spreads extremely rapidly where overcrowded conditions and poor sanitation occur: epidemics often occur in shanty towns, refugee camps and during large gatherings.
- ◆ The most effective way of preventing cholera is through improving sanitation and education about basic hygiene. A vaccine is available but is of limited value.
- ◆ Control of cholera can involve antibiotic treatment of sufferers and close contacts and isolation of cases.

develop. They are offered advice and counselling to allow them to come to terms with the disease and prevent them from infecting other people. Contacts of HIV positive people will often be traced in attempts to prevent further spread. In developing countries such services (including HIV tests) may not always be available.

To prevent the spread of HIV through blood and blood products Western countries have developed strict screening procedures. All blood used in transfusions, or for the extraction of products is now guaranteed to be free of HIV. Needles used for injections in hospitals and surgeries are sterile and are thrown away after one use. Drug addicts in many countries, including the UK, may be provided with free sterile needles and syringes. Unfortunately, due to lack of money and technology, and urgent demand for medical services, many developing countries do not have these controls. This means that HIV is still transmitted via blood transfusions, during routine hospital procedures, and even during vaccination programmes.

Drugs are now available to prolong the lives of AIDS sufferers, but the disease is currently incurable. There is, as yet, no vaccine against HIV. The main reason why development of a vaccine is difficult is that the virus is continually changing its surface antigens, making it hard for antibodies to recognise it and initiate mechanisms for its destruction before it enters the T cells. Furthermore, with such a dangerous virus there is concern over safety of the vaccine itself.

The ROLE of ANTIBIOTICS in the TREATMENT of INFECTIOUS DISEASE

An **antibiotic** is a molecule produced by one type of microorganism which is capable of destroying or inhibiting the growth of another type of microorganism. Most commonly they are chemicals produced naturally by fungi or bacteria which destroy other bacteria. Antibiotics work in several ways but they are often divided into two main categories: those which kill bacteria are called **bactericidal** antibiotics, whilst those which inhibit their growth are known as **bacteriostatic** antibiotics.

Today some antibiotics can be synthesised (made artificially) in laboratories, using the blueprint of natural molecules. Others are produced on a massive scale in fermenters which may use naturally occurring or genetically engineered microorganisms. In both cases production is highly efficient and cheap once the system is running.

The discovery of antibiotics was one of the most significant events in medical history. It was in 1928 that Alexander Fleming first noticed that the mould *Penicillium notatum* prevented the growth of bacteria on agar plates. Eleven years later, Ernst Chain and Howard Florey purified the antibiotic penicillin and tested it in mice with bacterial infections. By the mid-1940s several other antibiotics had been discovered and were being tested on human infections. Antibiotics were found to be extraordinarily efficient at killing bacteria and allowed the first effective cures for fatal diseases like syphilis and tuberculosis. They revolutionised the treatment of a wide variety of bacterial infections and have played a major role in preventing illness and death across the world. Many infections which we

◆ CHECKPOINT SUMMARY

- ◆ HIV/AIDS is caused by the HIV virus.
- ◆ AIDS is a disorder in which the body's immune system is gradually destroyed (by invasion and destruction of helper T-lymphocytes) leading to death from a range of infectious diseases.
- ◆ HIV/AIDS is a pandemic: 33 million people are affected with 2.6 million deaths in 1999.
- ◆ HIV virus is transmitted in three main ways: sexual contact, blood contact and from mother to child. Sexual contact is the most significant.
- ◆ HIV transmission can be reduced or prevented by changes in sexual behaviour; especially the use of condoms.
- ◆ Screening of blood products and use of sterile medical equipment prevents HIV spread in hospitals and other settings.
- ◆ There is, as yet, no HIV vaccine.
- ◆ Education about HIV/AIDS is critical in preventing further spread. The fact that the disease is sexually transmitted can make this more difficult. Counselling of people diagnosed as HIV positive (via HIV tests) is equally important in disease control.
- ◆ Differences in the availability of condoms, in adequate medical facilities and in education can help to explain why HIV/AIDS is spreading more rapidly in developing countries.
- ◆ Most new HIV/AIDS cases are in young heterosexuals in the developing world, but it is infecting increasing numbers in developed countries as well.
- ◆ HIV/AIDS has enormous social and economic significance: in addition to the deaths directly caused. It is affecting population structures, increasing the spread of some other infectious diseases and placing a strain on health budgets across the world.
- ◆ Infectious diseases are caused by pathogens which are usually bacteria, viruses, protoctists, and fungi. They remain the leading cause of death in many developing countries.
- ◆ Cholera, malaria, HIV and TB cause large numbers of deaths but are difficult to control.
- ◆ Disease prevention involves preventing people from becoming infected. Disease control involves managing people who do have the disease to prevent its spread.
- ◆ Social, economic and biological factors all have a role in prevention and control.

consider insignificant today, such as endocarditis (rheumatic fever) and the infections of wounds caused rapid death before antibiotics were discovered.

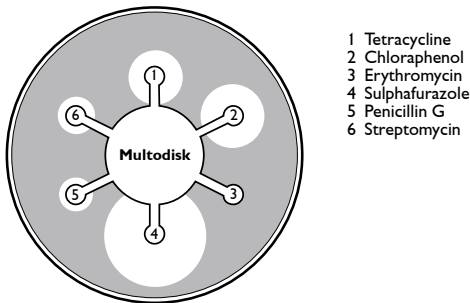
Antibiotics work by interfering with one or more of the essential functions of bacterial cells. They do not harm human cells due to the differences in cell structure between bacterial (prokaryotic) and animal (eukaryotic) cells. Antibiotics are usually specific to certain types of bacteria, and thus it is common practice to find out which bacterium is responsible for an infection before attempting to treat it. **Broad spectrum antibiotics** will work on all or most types of bacteria, but can be harmful as they also kill useful bacteria in the gut.

Antibiotics use one or more of the four main targets outlined below to attack bacterial cells:

- ▼ Interfering with production of the bacterial cell wall, particularly by inhibiting the formation of peptide cross-links within the wall, leading to cell breakdown (lysis) by osmosis as the delicate cell surface membrane cannot resist over expansion by the entry of water, without the surrounding cell wall.
- ▼ Damaging bacterial cell membranes.
- ▼ Limiting or preventing protein synthesis, especially the synthesis of enzymes.
- ▼ Limiting or preventing nucleic acid synthesis and hence cell division.

Antibiotic resistance has arisen over the past fifty years as a result of the excessive use of antibiotics. Such resistant bacteria acquire the ability to destroy the antibiotic, be impermeable to it, or have

Diagram to show action of specific antibiotics on a bacterial culture



sites normally targeted by antibiotics altered so that the antibiotic cannot interfere with cellular activities. All the antibiotics are therefore less effective, and some completely ineffective at killing the bacteria. Resistance may come in two main ways: through genetic mutations in bacterial DNA, or through introduction of resistance genes via other bacteria or viruses. The very short generation time and massive (asexual) reproductive potential of bacteria allows any beneficial mutations to be passed on very rapidly. (Some bacteria can divide to produce two new bacteria about once every 30 minutes, so that a single bacterium could theoretically result in a population of 2^{47} by the end of a 24 hour period.)

Two important examples of resistant bacteria (sometimes referred to as 'superbugs') are Multiple Resistant *Staphylococcus aureus* (MRSA) which is a common cause of infection in hospitals, and some strains of *Mycobacterium tuberculosis* which causes TB. Whilst random mutations of bacterial DNA which confer antibiotic resistance can occur at any time, the problem is made worse if courses of antibiotics are not completed or if sub-optimal doses are taken. A bacterium may, for example, require two specific mutations to make it fully resistant to an antibiotic. If one mutation offering partial resistance is acquired mid-way through a course of antibiotics the remaining days of treatment may eventually kill this bacterium even though they may do so more slowly than before. However, if the antibiotics are stopped, the bacterium with one mutation for partial resistance may acquire a second mutation. Together with the first this may offer total resistance. When 'multi-drug' treatments (many different types of antibiotic together) are used the chance of a bacterium developing resistance to all types at once is very low. But it is still possible because bacteria may pass genetic material from one to another. This is again more significant if courses are not completed and mixed populations of partially resistant bacteria occur together in a patient.

Antibiotic resistance is already responsible for increasing rates of illness and death from *Staphylococcus aureus*, and T.B. Health professionals are worried that the problem will increase if more bacteria become resistant to antibiotics, allowing common infections to once again become major causes of death across the world. They are calling for a reduction in the unnecessary use of antibiotics. This could include a reduction in the number of prescriptions of the drugs for minor infections in humans, and a reduction in the use of antibiotics in farming (60% of total antibiotic use) where they are added to feeds as growth promoters and to prevent disease.

◆ CHECKPOINT SUMMARY

- ◆ Antibiotics are substances produced by microorganisms which can kill or inhibit the growth of other organisms (usually bacteria).
- ◆ Bactericidal antibiotics kill other bacteria: bacteriostatic antibiotics inhibit the growth of other bacteria.
- ◆ Antibiotics are produced on a large scale using fermenters. Microorganisms producing them may be genetically engineered.
- ◆ Antibiotics were discovered in 1928 and have been in use since 1940s. Their use has caused an enormous reduction in severe illness and death from bacterial infections.
- ◆ Antibiotics interfere with essential functions of bacterial cells. They may upset synthesis of the bacterial cell wall, or prevent the production of proteins (enzymes) and nucleic acids.
- ◆ Antibiotics may be broad spectrum, killing most types of bacteria or specific to one particular species.
- ◆ Overuse of antibiotics in medicine and in farming industry has led to the emergence of some resistant strains of bacteria.
- ◆ Resistant strains of bacteria are not affected by antibiotics and hence can be very dangerous to humans as the infections they cause are untreatable and spread rapidly.
- ◆ Resistance often arises through random genetic mutations in bacterial DNA.
- ◆ Some strains of TB and *Staphylococcus aureus* are now resistant to all types of antibiotics. They are said to be 'multi-drug resistant'.

Immunity

Content

- ▼ The immune system
- ▼ The role of vaccination in controlling disease

Candidates should be able to:

- a) describe the origin, maturation and mode of action of phagocytes and lymphocytes.
- b) explain the meaning of the term immune response.
- c) distinguish between the actions of B lymphocytes and T-lymphocytes in fighting infection.
- d) appreciate the role of memory cells in long term immunity.
- e) relate the molecular structure of antibodies to their functions.
- f) distinguish between active and passive, natural and artificial immunity and explain how vaccination can control disease.
- g) discuss the reasons why vaccination has eradicated smallpox but not measles, TB, malaria or cholera.
- h) outline the role of the immune system in allergies, with reference to asthma and hay fever.

Introduction

Immunology is the name given to the study of the ways in which the immune system allows the body to protect itself from disease-causing organisms (**pathogens**) which have entered the body.

The human body is well adapted to prevent pathogens (mainly bacteria, fungi and viruses) from entering in the first place. There are several ways in which this is achieved:

- ▼ The skin forms a protective barrier against most pathogens. If it is cut, blood clotting helps to seal the wound and prevent pathogen entry.
- ▼ The mucus membranes of nose and respiratory tract filter the air using small hairs called cilia and trap pathogens in the sticky mucus for destruction by phagocytes.
- ▼ Anti-bacterial enzymes in saliva, sweat and tears help to destroy pathogens
- ▼ The stomach acid (pH 2) kills most pathogens which may enter via food or water

If however, these mechanisms fail and pathogens do enter the body tissues or blood, an **immune system** is necessary to attack and destroy these pathogens and so prevent serious disease or death. The immune system uses several specialised types of white blood cells, the most important being the phagocytes and the lymphocytes.

The ORIGIN, MATURATION and MODE of ACTION of PHAGOCYTES and LYMPHOCYTES

Phagocytes and lymphocytes, like red blood cells and platelets, are made by special cells known as **stem cells** found in the liver, spleen and bone marrow (tissue found in the centre of bones) of the fetus. In children they are found in the marrow of all bones, and in adults in the marrow of bones of the central skeleton, especially the sternum, the hip bone and the top ends of the femur (leg) and humerus (arm) bones.

The nuclei of stem cells are constantly dividing by mitosis to produce **identical** daughter cells. These cells all have the same genes and so have the potential to develop into any type of blood cell. They are said to be 'pluripotent'. Yet by expressing or 'switching on' different sets of these genes the daughter stem cells can differentiate into red blood cells, phagocytes or lymphocytes with their very different functions.

Phagocytes

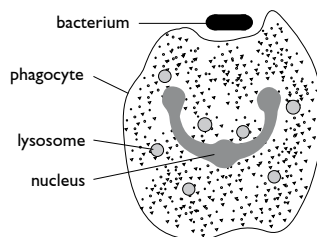
These are white blood cells (leucocytes) that can engulf and digest pathogens, other foreign material and dead or infected cells. They are **non-specific** in their actions so will deal with any type of foreign material which they come across. They have a distinctive appearance with a lobed nucleus and grainy cytoplasm. Phagocytes are mainly found in the blood and the lymphatic system, especially in the lymph nodes. They are also capable of squeezing through the tiny gaps between cells in the walls of capillaries and entering the tissue fluid which surrounds every cell. This is important as it allows the phagocytes to act in any body tissue which becomes infected with pathogens. Phagocytes are also found in the alveoli of the lungs where they attack pathogens entering via the air.

Lymphocytes

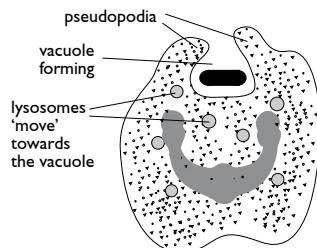
These are white blood cells that are involved in very **specific** immune responses against pathogens. They do not engulf and digest pathogens, but use other, more complicated processes to destroy them. Like phagocytes, lymphocytes circulate in the blood and lymph fluid and are also found within the lymph nodes. They have a large rounded nucleus which almost fills the cell and a small amount of non-grainy cytoplasm.

Having developed in the bone marrow, lymphocytes move through the body to the spleen and lymph nodes where they mature and become active. Some of these lymphocytes move directly to the spleen and lymph nodes and are known as **B-lymphocytes** or B-cells. Other lymphocytes move to the spleen and lymph nodes via the thymus (a gland found beneath the sternum at the top of the chest) where they undergo further differentiation. These develop into **T-lymphocytes** or T-cells (T for thymus).

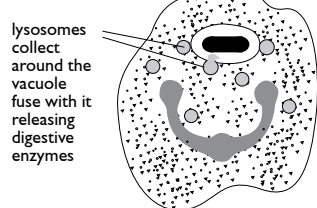
Phagocyte 'moves' towards bacterium



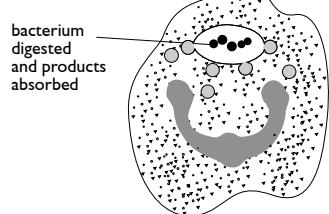
Vacuole forming



Vacuole formed



Lysosomes fuse with vacuole and release enzymes



The IMMUNE RESPONSE

B-lymphocytes and T-lymphocytes both respond to the presence of specific types of foreign material in the body and bring about actions to remove them. Such foreign material includes pathogens as well as 'non-self' human cells (such as the cells of blood or organs transplanted from other people) and substances in certain foods or other materials which bring about allergic reactions. Although B-lymphocytes and T-lymphocytes work in very different ways, the starting point for both is the recognition of an **antigen**. With regard to pathogens, antigens are surface protein molecules which trigger an immune response.

The ACTIONS of B-LYMPHOCYTES and T-LYMPHOCYTES

B-lymphocytes

The function of B-lymphocytes is to produce antibodies in response to antigens in a process known as **humoral immunity**. On the cell surface membrane of B-lymphocytes are a number of specific **antigen receptors** or membrane bound antibodies. These are sites to which antigens on the surface of pathogens may become attached, leading to a sequence of events in which free antibodies are produced to prevent the pathogens from causing harm.

There are many thousands of specific types of B-lymphocyte and each is capable of recognising only one specific antigen from a pathogen. For example, there is one type of B-lymphocyte which will attach to the bacterium causing TB, another type which will attach to the bacterium causing cholera and so on. This specificity is due to slight differences in the shape of the antigen surface receptor protein on each type of B-lymphocyte.

Sequence of events in humoral immunity:

- ▼ Pathogen enters body. This may be via droplets in air, via a vector, in food or water, or via body fluids such as saliva, blood or semen.
- ▼ Antigens on surface of pathogen come into contact with their specific antigen receptor on a B-lymphocyte.
- ▼ Binding of antigen to antigen receptor activates the B-lymphocyte and causes it to divide producing a clone of identical B-lymphocytes.
- ▼ Most of the B-lymphocytes turn into **plasma cells** and the rest turn into **memory cells**.
- ▼ The plasma cells begin to secrete specific antibodies against the pathogen concerned. Antibody molecules are secreted at a very high rate: up to 30 000 molecules per second.
- ▼ The antibodies attach to the antigens on the pathogen and lead, indirectly, to the destruction of the pathogen. (See later for details).

◆ CHECKPOINT SUMMARY

- ◆ The body protects itself from becoming infected but has an immune system to attack and destroy any pathogens which do enter.
- ◆ Immunity is associated with white blood cells, particularly the phagocytes and lymphocytes.
- ◆ Phagocytes and lymphocytes are derived from stem cells.
- ◆ Stem cells are found in the liver, spleen and bone marrow.
- ◆ Stem cells are pluripotent: they can divide to form any of the different blood cell populations.
- ◆ Phagocytes are characterised by a lobed nucleus and grainy cytoplasm.
- ◆ Phagocytes engulf and digest pathogens in a non-specific fashion.
- ◆ Phagocytes are found in blood as well as other tissues.
- ◆ Lymphocytes are characterised by a large dense nucleus and non-grainy cytoplasm.
- ◆ There are B and T lymphocytes, both of which are involved in specific immune responses.
- ◆ After maturing in bone marrow, lymphocytes migrate to the lymph nodes.
- ◆ B-lymphocytes migrate directly, T-lymphocytes move via the thymus gland.
- ◆ Lymphocytes are found in blood and lymphatic system, especially in lymph node.

◆ CHECKPOINT SUMMARY

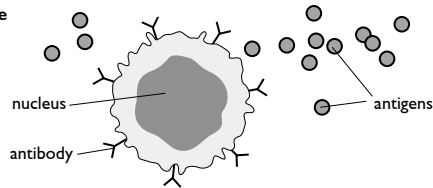
- ◆ B and T lymphocytes recognise foreign material in the body.
- ◆ Foreign material is detected by the presence of foreign surface antigens.
- ◆ Antigens are usually protein molecules found on the surface of all cells which may be pathogens or other human cells. Viruses and non-living material may also possess antigens.
- ◆ An immune response occurs when lymphocytes detect the presence of foreign antigens and set in motion mechanisms to destroy the foreign material.
- ◆ The immune system is important in protecting the body from the damaging effects of pathogens and other foreign materials.

- ▼ Once the pathogens have been destroyed, the plasma cells eventually die and secretion of antibodies stops. But the memory cells remain in the lymph nodes and the circulation in case of a further infection with the same pathogen.

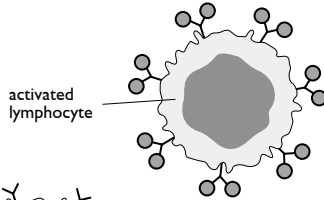
N.B. The above gives the sequence of events in response to a pathogen. It would be similar for any other foreign cell or foreign antigen.

Humoral Immunity

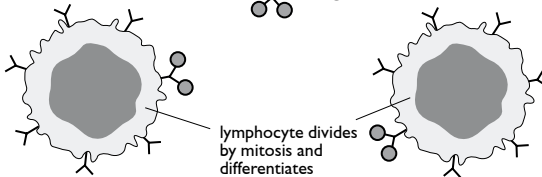
Immature B lymphocyte



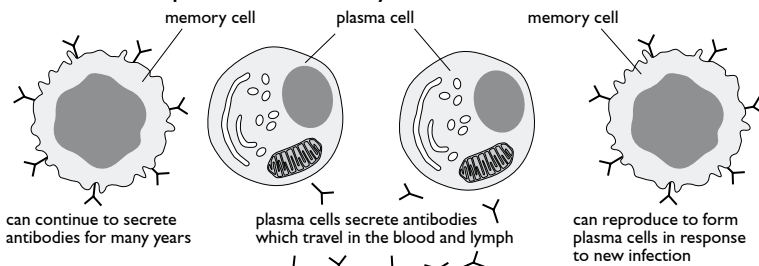
Activation



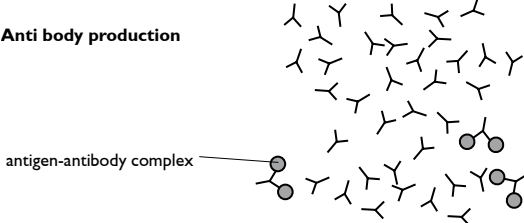
Division



Differentiation into plasma cells and memory cells



Anti body production



T-lymphocytes

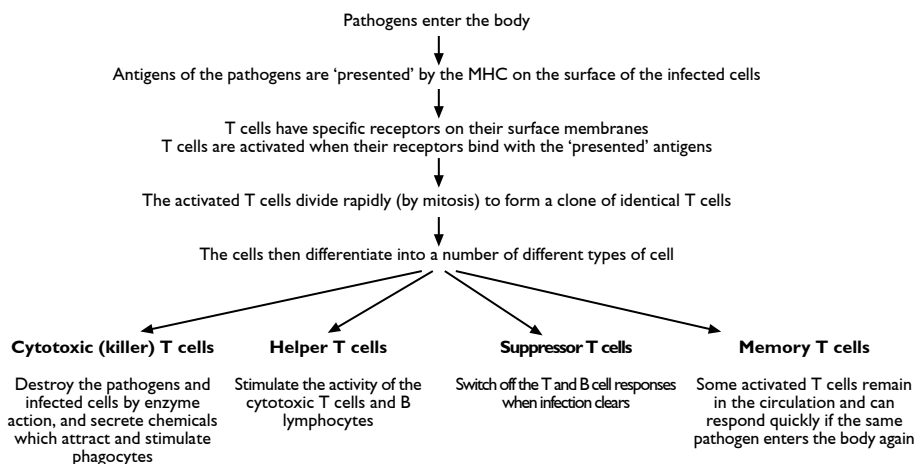
T-lymphocytes are involved in a different form of immunity known as **cell mediated immunity**. They do not produce antibodies but work directly on infected cells. As with B-lymphocytes, there are thousands of different types of T-lymphocyte each of which only recognise one specific antigen.

T-lymphocytes, like B-lymphocytes, have antigen receptors on their surface. However, unlike B-lymphocytes they cannot recognise antigens from pathogens on their own. They can only recognise them when they have been **processed** by human cells and **presented** on the surface of these cells. This procedure relies on a group of special proteins called the **Major Histocompatibility Complex (MHC)** which are present on the surface of all human cells.

Normally the MHC allows the body's immune system to recognise its own cells and prevent their destruction. However, if a human cell becomes infected with a pathogen, then antigens from this pathogen interact with the MHC molecules and attach to them. They are now 'presented' on the surface of the cell. This alerts the body's immune system to the presence of the pathogen and allows T-lymphocytes to destroy the cell. The cell is known as an **antigen presenting cell**.

Antigens may also be presented by MHC molecules on the surface of B-lymphocytes and phagocytes which are also known as antigen presenting cells. This is important as it allows the different parts of the immune system to **cooperate** with each other. Thus at the same time as producing antibodies, a B-lymphocyte can be presenting an antigen on its MHC and activating T-lymphocytes.

Cellular Response to infection - T Lymphocytes (T cells)



Sequence of events in cell mediated immunity:

- ▼ Pathogen enters body.
- ▼ Antigens of pathogen which are presented by the MHC on a body cell come into contact with specific T-lymphocyte receptors which recognise them
- ▼ T-lymphocyte binds to presented antigen on infected cell via antigen receptor
- ▼ T-lymphocyte is activated and divides to form a clone of identical T-lymphocytes which enter the circulation and can attach to other infected cells
- ▼ T-lymphocytes destroy the pathogens inside the cells to which they are bound. Some do this by releasing lytic enzymes into the infected human cells. Others release chemical messengers called cytokines which attract phagocytes to engulf the cells
- ▼ Some T-lymphocytes then turn into memory cells which remain in circulation and in the lymph nodes in case of further infection.

Helper and Suppressor T-lymphocytes

The T-lymphocytes described above are called **cytotoxic T-lymphocytes**. There are also two other types of T-lymphocyte which work in different ways. **Helper T-lymphocytes** 'help' B-lymphocytes and cytotoxic T-lymphocytes to function by releasing chemicals called cytokines and interleukins which stimulate the activity of the lymphocytes. They are only able to do this once they have been activated by binding to an antigen presented on an antigen presenting cell (It is these T-lymphocytes which are destroyed by the HIV virus, resulting in a depression of immunity). **Suppressor T-lymphocytes** are important in switching off the B- and T-lymphocyte responses to a particular pathogen once the infection has been cleared.

◆ CHECKPOINT SUMMARY

- ◆ The type of immune response associated with B-lymphocytes is termed humoral immunity and involves the production of antibodies.
- ◆ There are thousands of different types of B-lymphocyte, and each type will only recognise one specific type of antigen.
- ◆ B-lymphocytes have antigen receptors which detect and bind to foreign antigens.
- ◆ Binding of antigen to antibody activates the B-lymphocyte, causing it to divide.
- ◆ B-lymphocytes in the clone divide into either plasma cells or memory cells
- ◆ Plasma cells secrete specific antibodies against the pathogen
- ◆ Memory cells remain in the body in case of future infection with the same pathogen.
- ◆ T-lymphocytes are associated with cell mediated immunity: the direct killing of infected cells.
- ◆ As with B-lymphocytes, there are many types of T-lymphocytes, each being specific to one antigen.
- ◆ T-lymphocytes can only recognise foreign antigens when presented on the surface of a human cell by an MHC molecule. Recognition involves specific antigen receptors.
- ◆ When a T-lymphocyte is activated by binding to its specific antigen it will proliferate to form a clone of identical cells.
- ◆ T-lymphocytes may destroy infected cells by releasing lytic enzymes.
- ◆ There is co-operation between T-lymphocytes and other components of the immune system including helper and suppressor T lymphocytes, phagocytes and B-lymphocytes.

MEMORY CELLS and LONG TERM IMMUNITY

Both B-lymphocytes and T-lymphocytes form memory cells after encountering a pathogen in the body. The function of these is to allow the body to 'remember' pathogens it has encountered before and produce a much faster immune response to them the second time around.

When a familiar antigen is encountered, T-lymphocyte memory cells will divide to form functional T-lymphocytes, which enter the circulation and move to the area of infection. They are known to move preferentially to the area of the body where they encountered that specific infection before.

Similarly, B-lymphocyte memory cells will divide and form new antibody producing plasma cells when they encounter their familiar pathogen. In each case, some memory cells will always be left so that the body can respond to any number of future infections with the same pathogen.

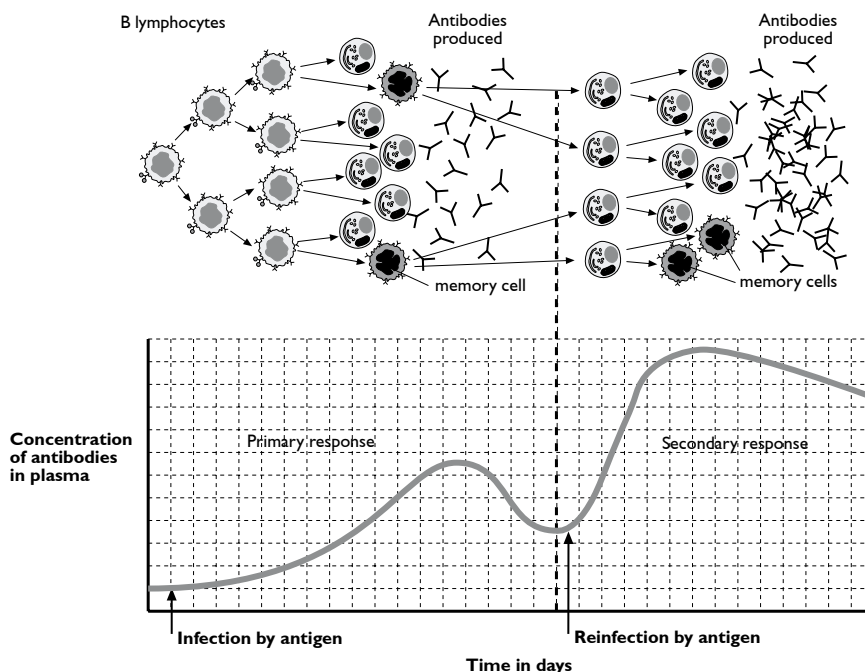
Two main differences exist between the first or **primary response** by B-lymphocytes to a pathogen, and the **secondary response**.

Antibodies are produced more rapidly in the secondary response.

Larger amounts of antibodies are produced in the secondary response.

◆ CHECKPOINT SUMMARY

- ◆ Both B and T-lymphocytes form memory cells during a first encounter with an unfamiliar pathogen. These remain in the body in case of future encounters with the same pathogen.
- ◆ Memory cells are activated if the pathogen is encountered again.
- ◆ T-lymphocyte memory cells divide to form new functional T-lymphocytes.
- ◆ B-lymphocyte memory cells form new plasma cells which secrete antibodies.
- ◆ The secondary antibody response is more rapid and larger than the primary response.
- ◆ Memory cells can provide life-long immunity to some pathogens but not to others.
- ◆ The production of memory cells can be stimulated naturally or artificially via vaccination.



The presence of memory cells means that with some diseases such as mumps or chicken pox one infection can make a person **immune** to that infection for the rest of their life. The pathogens causing these diseases will almost certainly get into their body again during that time, but the immune response is so rapid that they will not become ill. With other infections, such as malaria, and influenza, people can suffer many bouts of illness from the same type of pathogen. This is because such pathogens have a very high mutation rate in the genes coding for antigen proteins. The structure of the antigens changes slightly and the memory cells fail to recognise it.

The STRUCTURE and FUNCTION of ANTIBODIES

Antibodies are molecules released by B-lymphocytes in response to specific antigens. They are found in the blood plasma and are a type of protein molecule known as **immunoglobulins**.

Each antibody consists of four polypeptide chains which are folded to form a molecule shaped like a Y. The straight tail of the Y is known as the **constant region** and is the same in every type of antibody. The forked part of the Y is known as the **variable region** as this is the part which varies slightly in shape between each type of antibody.

Differences in the amino acid sequence of the polypeptide chains which make up the variable region create antigen binding sites of different shapes. Each antibody thus has the ability to bind only to antigens of corresponding shape to itself. (Antibodies may be thought of as keys which will only fit into the locks of specific antigens). For example, an antibody with the specific shape to bind to the TB causing bacterium will not bind to antigens on the bacterium which causes cholera.

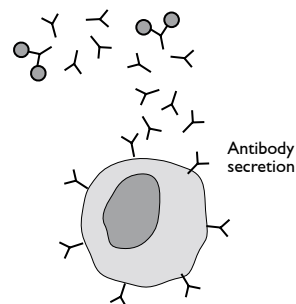
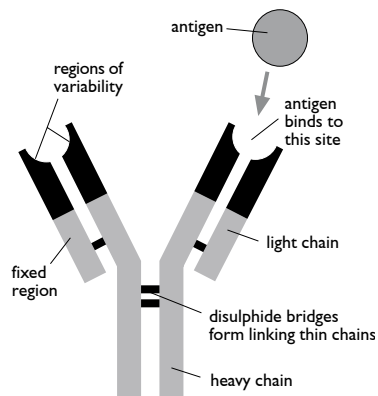
There are three main ways in which antibodies help to destroy pathogens:

- ▼ By coating pathogens and causing them to stick together in such a way that they can then be engulfed by phagocytes.
- ▼ By binding to pathogens at sites which interfere with their activities. For example, by covering the protein coat of a virus and preventing it from attaching to host cells.
- ▼ By stimulating other blood components called **complement** to destroy the pathogen.

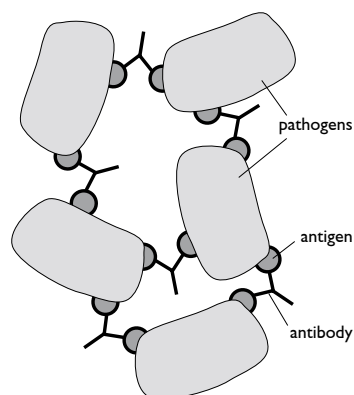
◆ CHECKPOINT SUMMARY

- ◆ Antibodies are produced by plasma cells when in response to specific antigens.
- ◆ Antibodies are a type of globular protein molecule called immunoglobulins which are made up of 4 polypeptide chains.
- ◆ Antibodies are shaped like a Y. The tail of the Y is the constant region and is always identical.
- ◆ The fork of the Y is the variable region and contains the antigen binding site: it varies between antibodies giving them specificity to certain antigens.
- ◆ Antibodies do not directly destroy pathogens but achieve this in interaction with other components of the immune system.

Structure of an antibody



Pathogens trapped ready for phagocytosis



TYPES OF IMMUNITY

Active immunity

The type of immunity to a disease which follows a natural infection with a pathogen is known as **natural active immunity**. As described above it involves a pathogen entering the body and stimulating the production of memory cells for future protection against the same disease. The person does not necessarily have to get ill from the infection for the immune system to work in this way.

Vaccination

This works in a similar way to natural active immunity. A person is given a very small dose of the pathogen or a 'toxin' produced by the pathogen to which immunity is required. Usually this is in the form of an injection, but oral vaccines also exist for some diseases. This type of immunity is known as **artificial active immunity**, since the pathogen is introduced to the body in an artificial manner and the person does not usually get ill from the disease as they often do in natural active immunity. Following vaccination, B-lymphocytes are stimulated to produce plasma cells and hence antibodies, and memory cells. T-lymphocytes may also be stimulated and produce memory cells. These memory cells remain in the body and allow the person to respond quickly if they encounter the same pathogen again, preventing them from becoming ill.

If a vaccine contains the pathogen itself, the pathogen may be dead or living. If living, there is a risk of causing illness from the vaccination, thus the pathogen used is often a naturally occurring mild strain, or it has been attenuated (weakened) in some way to reduce its virulence, its growth rate, or both. Recently this has been achieved by genetically engineering pathogens. In rare cases, a closely related pathogen to the one for which immunity is sought, has such similar antigens that it may be used instead. This was the case with the early smallpox vaccines which were made from the cowpox virus. Some very new genetically engineered vaccines, including the hepatitis B vaccine do not use a pathogen at all: instead genes controlling the production of antigens are transferred from the virus to cells of a micro-organism (such as yeast) where the antigen can be produced safely in culture.

Some vaccines provide complete immunity after a single dose. Others require a second dose known as a 'booster' to allow a greater number of memory cells to form.

Vaccination is a very safe way of gaining immunity to diseases which might otherwise cause serious illness or death if caught naturally. It has had an enormous impact in reducing death and debilitation from infectious disease in childhood. In countries where there seems to be little threat of diseases like measles some parents may be reluctant to have their child vaccinated. Whilst there may be reasons for this, such practice undermines the effectiveness of vaccine programmes. However, in the developing world vaccination can carry the serious threat of infection with HIV/AIDS via the reuse of needles.

Passive immunity

This is the process whereby ready made antibodies are given to a person to offer them rapid but short-term immunity to a disease. It is called passive because the person plays no role in actually producing the antibodies against that disease. Since memory cells are not given nor their production stimulated, such passive immunity will only last a few weeks or months, after which time the antibodies will be broken down by the body and stop working. There are two types of passive immunity.

Natural passive immunity

This occurs when antibodies are passed from mother to fetus via the placenta, or from mother to baby via the colostrum (first milk). These antibodies protect the baby from diseases which it may encounter in the first few months of life before its own immune system starts functioning properly.

Artificial passive immunity

This occurs when antibodies produced in another organism are injected into a person to give them short term protection against a specific disease. Antibodies may be given to a person who has already got the disease (such as someone who has got rabies from a bite by an infected dog) or to a person who is at risk of a catching a disease such as tetanus. In the past, such antibodies could only be obtained from the blood of other animals (who had been infected with the pathogen) in the form of 'anti-serum' (serum being the blood plasma without its large proteins).

Now some of the antibodies required for passive immunisation are produced as **monoclonal antibodies** in the laboratory. These are antibodies produced by a single clone of identical B-lymphocytes (plasma cells). They are produced by cells known as **hybridomas** which are created in the laboratory by fusing a plasma cell of the desired type (one that produces antibodies against a specific pathogen) with a cancer cell (myeloma). The hybridomas have the dual ability to constantly divide, like a cancer cell, and to produce antibodies like a plasma cell. The monoclonal antibodies produced have a variety of uses in medicine, research and diagnostic tests.

The use of vaccination in controlling disease.

The principle of vaccination was first demonstrated scientifically by Edward Jenner in 1796. Jenner infected a young boy with cowpox (by scratching the boy's skin and inserting some pus from a cowpox pustule) and made him immune to the related but deadly disease, smallpox. In performing this potentially hazardous experiment, Jenner was exploiting local knowledge regarding the immunity of milk maids to small pox owing to their regular contact with the cowpox virus. His work had an enormous impact, since at that time smallpox was a major killer and about a quarter of people who caught the disease died.

Since Jenner's time, and especially in the past one hundred years when the pathogens causing most infectious diseases have been identified, many different vaccines have been produced. Such vaccines have played a major role in reducing the number of deaths

from infectious diseases such as, polio, measles, and TB, although only in the case of smallpox has a vaccination programme led to the complete eradication of a disease.

In Britain today, most young children are vaccinated against a variety of diseases including measles, mumps and *Rubella* (MMR), diphtheria, tetanus and whooping cough (DTP) and polio. Later on they receive vaccines against TB, and possibly other diseases such as hepatitis, yellow fever, typhoid and cholera if travelling abroad.

Whilst vaccination is important in protecting individuals against disease, it is more significant in terms of controlling the disease in the whole population of a country or region. In 'controlling' a disease, a vaccination programme aims to reduce the number of cases of illness and death from the disease to a low level, to ensure that there are few infectious carriers of the disease in the population and few non-immune people who are susceptible to the disease.

Success in disease control, and ultimately in disease eradication, will only be achieved if the vast majority of people in the country (or in the whole world in the case of eradication programmes) cooperate and agree to be vaccinated. In order for this to occur, the government of the country must actively promote vaccination, or even make it compulsory. Vaccination should be free and easily available to all people in the population. In addition, the population must be educated about the disease and the vaccine so that they appreciate the importance of the vaccination.

It is, however, very difficult to meet all of these conditions, even if there is money and government support for the vaccination programme. Firstly, the populations of countries and regions are always changing: new people are born, old people die and people migrate into and out of the area, altering the proportion of those with immunity to the disease. Secondly, some people will not agree to vaccination as they believe that the vaccine itself can cause illness or even death. Thirdly, some diseases, for example tetanus, can exist in other animals (animal reservoirs) and/or in the soil. This means that even if everybody is vaccinated it is very unlikely that the disease could ever be eradicated.

The EFFECTIVENESS of VACCINATION in ERADICATING and CONTROLLING DISEASE

Smallpox

This is caused by the *Variola* virus, and was declared officially eradicated (absent from all human populations and from anywhere else in the environment) in 1979, so people are no longer vaccinated against this disease. This is the only example of a disease being eradicated by human intervention. The eradication programme required a huge amount of funding as well as close international cooperation. There were several features of the disease which helped to make the eradication effort successful:

- ▼ Smallpox was a very recognisable disease. People were familiar with the symptoms.
- ▼ Smallpox had no long term carriers (people who showed no

◆ CHECKPOINT SUMMARY

- ◆ Natural active immunity, involving memory cells, results from a natural infection with a pathogen.
- ◆ Artificial active immunity, which also involves memory cells, is provided by vaccination.
- ◆ Vaccination is the process whereby a small quantity of material from a pathogen is deliberately introduced into the body in order to stimulate lymphocytes to make an immune response.
- ◆ Vaccines may contain dead pathogens, live attenuated pathogens, or toxins or antigens from pathogens.
- ◆ Genetic engineering is used in the production of some vaccines.
- ◆ Vaccines generally provide a safe and effective way of gaining immunity to a disease.
- ◆ Passive immunity involves the provision of ready made antibodies to a person.
- ◆ Passive immunity does not stimulate lymphocytes or memory cells. It is short term.
- ◆ Natural passive immunity is provided for a fetus when antibodies cross the placenta, or for a baby via antibodies in colostrum.
- ◆ Artificial passive immunity involves a person being injected with antibodies against a disease he/she has or is at risk of in the short term.
- ◆ The principle of vaccination was first scientifically demonstrated by Jenner in 1796.
- ◆ Since Jenner, vaccination has had a dramatic impact on deaths from a range of infectious diseases, especially in childhood.
- ◆ A vaccination will prevent an individual getting ill or dying from an infectious disease but it can also control the disease within the community or region if people cooperate.

symptoms of illness but were still infectious, as may happen with TB, malaria and cholera).

- ▼ The smallpox virus could only be spread directly from one person to another. It could not survive in any other animal, in the water or the soil. This limited its rate of survival and spread.
- ▼ The smallpox vaccine was very effective and provided total life long immunity (as did natural infection in those who survived). Vaccination created a distinctive scar on the arm, marking those already vaccinated. No 'booster' vaccines were needed.
- ▼ The smallpox virus was very stable. Unlike the HIV virus and the protocist malaria parasite, its genes did not mutate and change its surface antigens.

The success of vaccinations against other diseases has been mixed. The measles and TB (BCG) vaccines have been very successful in reducing illness and death, while the cholera vaccine has been used in only a limited way. There is still no effective malaria vaccine. Reasons for such variations in the effectiveness of vaccination programmes relate to the types of pathogens involved, their means of transmission, the nature of the diseases caused and financial and political considerations.

Measles

A measles vaccine has been around for almost fifty years and saves millions of lives per year, yet the disease still occurs all over the world and kills many children in the developing world. Reasons for this include:

- ▼ Measles is one of the most highly infectious diseases being passed by droplet infection from one person to another very rapidly
- ▼ To eliminate the disease over 95% of children in towns must be vaccinated. But the rate is usually lower as some parents believe that there is a risk of illness or death from the vaccine
- ▼ In the developed world the disease rarely causes death, so people regard vaccination as less important than for other diseases.

Tuberculosis (TB)

TB vaccine (the BCG vaccine) only appeared in the 1930s after the number of deaths and illnesses from TB had already declined dramatically following improvements in living and working conditions. Since 1950 it had been used extensively and has been an important tool in TB prevention and control, yet eradication of TB is unlikely for the following reasons.

- ▼ People without symptoms of TB may be carriers and can transmit the disease (via droplets) for many years, making it harder to trace the spread of infection
- ▼ TB is not very recognisable, and people in the developed world have stopped thinking of it as an important disease. For example, vaccination in some parts of the UK stopped for a few years in the early 1990s
- ▼ The TB vaccination is not 100% effective
- ▼ A form of TB, *Mycobacterium bovis*, exists in cattle and can be transmitted to humans via unpasteurised milk.

Malaria

Malaria has defied attempts to develop an effective vaccine despite decades of research. The main reasons for this are:

- ▼ DNA of the malaria parasite, has a very high mutation rate and its antigens (encoded by genes) are always changing. The antibodies and memory cells produced by a vaccination may not be effective against new malaria infections where antigens have changed
- ▼ Malaria parasites live in the liver cells and red blood cells of humans. Inside the red blood cells, where they spend the majority of their life cycle they cannot be targeted by either antibodies or T-lymphocytes
- ▼ Humans without disease symptoms often have huge numbers of the parasites in their blood and can thus act as carriers who can pass the disease on to others via female mosquitoes
- ▼ The disease is spread from person to person by the female *Anopheles* mosquito vector which can travel over large distances. This vector has proved very difficult to control in most areas.

Even if a vaccine was available, there might also be logistical and financial problems in vaccinating against malaria which is very widespread in the poorest countries of the developing world.

Cholera

Cholera vaccination has not been very significant in the control of cholera, and eradication of the disease will not occur with the vaccines that are currently available. Cholera is primarily a disease of poverty and responds best to improvements in sanitation, hygiene and living conditions. The importance of vaccination is limited by the following:

- ▼ The bacterium causing cholera (*Vibrio cholerae*) is spread by the faeco-oral route, (via faecal contamination of water or food sources) allowing the infection to spread very rapidly from one person to hundreds or thousands of others
- ▼ Cholera exists in carriers who have no symptoms but still transmit the disease
- ▼ The vaccination that is currently available is not very effective. It uses heat-killed rather than live bacteria and provides only partial protection for a few months. (It is hoped that a new vaccine containing live genetically engineered bacteria will be more effective).

◆ CHECKPOINT SUMMARY

- ◆ Only one disease has been eradicated by vaccination: smallpox, declared eradicated in 1979.
- ◆ Biological reasons for smallpox eradication include the fact that the disease was recognisable, the virus was very stable, had no non-human reservoirs or long term carriers. The vaccine was very effective, provided life-long immunity, and created a distinctive scar.
- ◆ Economic/political factors included a highly coordinated international eradication programme.
- ◆ The success of smallpox eradication has not been repeated for other diseases. Reasons for this are social and economic as well as biological.
- ◆ Measles is highly contagious with a short incubation period. Eradication would require over 95% of people to be vaccinated in all regions. This is highly unlikely in the developed world as the disease is not always considered serious and parents opt out of vaccination.
- ◆ So far it has not been possible to produce an effective malaria vaccine. One reason for this is that the malaria parasite constantly changes its surface antigens, preventing memory cells from functioning effectively. It is also a vector borne disease occurring in poor countries.
- ◆ Cholera is a highly contagious disease with symptomless carriers and non-human reservoirs. It is a disease of poverty and would be most effectively controlled by improved sanitation. The current cholera vaccine, using a dead bacterium does not provide complete immunity.
- ◆ Tuberculosis has both symptomless human carriers and a non-human (bovine) reservoir. It is not always recognisable in early stages, and had ceased to be considered important in the developed world until a few years ago. The vaccine is not 100% effective

The ROLE of the IMMUNE SYSTEM in ALLERGIES: with REFERENCE to ASTHMA and HAY FEVER

In addition to their specific B- and T-lymphocyte responses to pathogens, humans are also capable of inflammatory responses to unusual antigens in their environment which are not associated with pathogens, such as the toxins in bee stings or insect bites. If, for example, a person is stung by a bee, the toxins stimulate the production of a chemical called **histamine** from mast cells in the skin and connective tissue around the site of the sting. The area becomes warm and swollen with fluid since histamine increases the

flow of blood to the region and makes the walls of capillaries more permeable, allowing tissue fluid containing white blood cells to leak out. This not only brings phagocytes to the site, but also helps to dilute any toxins present.

This normal, protective response to unusual antigens is an important part of the body's immune system. In some individuals, however, the immune system responds **vigorously** and **inappropriately** to antigens on the surface of common materials, leading to severe inflammatory reactions and even death. This is the basis of **allergies**. The substances which cause allergies or allergic reactions are known as **allergens**. These may be living things, such as pollen, or non-living things without protein based antigens such as food additives or some metals. It is not known why some people react to these allergens and others do not, but genetic factors are likely to play a role.

In all types of allergies, antigens on the surface of certain allergens, such as pollen, peanuts or cat fur, stimulate the production of allergen-specific antibodies known as **IgE antibodies**. These in turn bind to and stimulate **mast cells** to produce **histamine**, often in many parts of the body at once.

Hay fever

This is a very common allergy which is more common in the summer. Antigens on pollen grains from wind pollinated flowers are detected by mast cells, especially those in the nose and eyes. The histamine produced causes the eyes and the lining of the nose to become itchy and to swell up, often leading to sneezing. Excess fluid is released from the tissues causing a 'runny nose' and watering eyes. In some people the pollen antigens also cause the skin to become itchy and swollen and trigger reactions in the lungs leading to asthma.

In most cases of hay fever, common drugs known as '**anti-histamines**' will rapidly reverse the effects of the histamine and reduce the swellings and irritation.

Asthma

This can be defined as difficulty in breathing caused by constriction (narrowing or closure) of the bronchioles in the lungs. This makes it difficult for air to enter and leave the lungs and sufferers feel 'short of breath'. There are several causes, but one of the most common is an allergic reaction to a specific antigen. Antigens on pollen grains, on dog or cat hair, and on certain foods such as eggs or peanuts may stimulate mast cells in the respiratory tract (trachea and bronchioles) to release histamine. The histamine has three main effects, all of which result in a reduction of the diameter of the bronchioles within the lungs and a consequent reduction in the flow of air into and out of the lungs:

- ▼ the lining of the bronchioles swells up
- ▼ the lining of the bronchioles begins to secrete excess mucus
- ▼ the smooth muscle in the walls of the bronchioles contracts.

In severe cases of asthma the swollen bronchioles allow such a minimal amount of air to reach the alveoli that death by suffocation can occur. Usually, however, drugs known as 'bronchodilators' taken via inhalers can rapidly reverse the effects of the constricted bronchioles.

◆ CHECKPOINT SUMMARY

- ◆ Protective inflammatory responses occur when non-pathogenic antigens (eg. toxins in bee stings) are encountered. This leads to swelling and leakage of tissue fluid in affected areas.
- ◆ In some individuals severe (even life-threatening) inflammatory responses are stimulated by antigens on common materials such as pollen and some foods. This is the basis of allergies.
- ◆ Hay fever is a common allergy caused by antigens on pollen grains. Specific IgE antibodies are produced in response. These bind to mast cells and cause release of histamine.
- ◆ Histamine causes irritation and swelling of the mucous membranes of eyes and nose and release of excess fluid. The skin and lungs may be affected.
- ◆ Hay fever can be treated with anti-histamine drugs.
- ◆ Asthma is a difficulty in breathing caused by constriction of bronchioles.
- ◆ Asthma can result from allergic reactions. Histamine causes the linings of the bronchioles to swell, and secrete excess mucus and causes the smooth muscle in the walls of the bronchioles to contract. All three features reduce air flow into and out of lungs.
- ◆ Drugs to reverse these effects, 'bronchodilators' can be taken via inhalers.